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(54) Title: TABLET FOR PROPHYLAXIS AND TREATMENT OF DENTAL AND PERIODONTIUM DISEASES

(57) Abstract: The invention relates to stomatology and specifically to tablet for prophylaxis and treatment of dental and periodontium diseases. The tablet contains following components at a ratio, wt %: Magnesium sulfate or magnesium chloride or magnesium lactate or magnesium oxalate: 3.26-5.26, Pyridoxine hydrochloride: 0.060-0.074, Thiamin mononitrate: 0.50-0.062, Calcium glycerophosphate: 30.0-38.9, Ground laminaria thallus or dried laminaria aqueous extract: 1.1-2.2, Stevioside: 0.3-0.9, Sorbitole: 10.0-25.0, Xylite: 10.0-25.0, Auxiliary components: 15.62-45.42



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**Tablet for prophylaxis and treatment of dental  
and periodontium diseases**

**Field of application**

5           The invention relates to medicine or rather to stomatology, in particular to tablet for prophylaxis and treatment of dental and periodontium diseases.

**Background of invention**

10           Prophylaxis of oral diseases including dental caries has been a matter of long and continuous interest of scientists and experts. Fluor is known for its prophylactic and anti-cariou effect. It reduces caries morbidity by 30-45% entering with drinking water, fluorated milk and salt. Herewith it is more effective along with sufficient calcium content in drinking water. (Yu.A. Fedorov Prophylaxis of dental and oral cavity diseases. L.:Meditsina, 1979, pp32-35).

15           Hopeful results were obtained while using vitamins B<sub>1</sub> and B<sub>6</sub>. ( Yu.A. Fedorov Clinical course and treatment of hypersensitivity of hard tooth tissues, L.:Meditsina, 1970, pp 94-95). Rather contradictory data about prophylactic action of microelements were specified in the following research papers: Yu.A. Fedorov Prophylaxis of dental and oral cavity diseases. L.:Meditsina, 1979, pp34-38; N.A. Kodola Microelements in  
20           prophylaxis of teeth caries, Kiev, Zdorovie, 1979, pp 110,117,122. Alongside there were represented investigation results pointing to constant mineral renewal of teeth tissues through ingress of micro- and macroelements from saliva, drink and food. This physiological process renders it possible to prevent and even treat dental diseases like for example, hypersensitivity. (Yu.A. Fedorov Clinical course and treatment of  
25           hypersensitivity of hard tooth tissues, L.:Meditsina, 1970, pp105-107).

          There is known formulation in the form of tablets of sodium fluoride thoroughly used in stomatology. Among disadvantages of this medication there are listed the following:

- it is difficult to control total fluor ingress from various sources;
- 30           - it does not have integrated effect since it lacks anti-inflammatory function;
- there are use limitations for elder patients.

According to a number of authors fluoride can reduce bone strength especially in a state with high metabolism speed. (Riggs B.L., Melton III L.G. Osteoporosis – tr. from Eng. M-Spb: ZAO Izdatelstvo Binom, Nevski Dialekt, 2000, p441).

It is known that combined application of endogeneous calcium medications and local formulation makes it possible to increase treatment efficacy. (Yu. A. Fedorov, V.A. Drozhzhina Clinical course, diagnostics and treatment of noncarious lesions of teeth. *Novoe v stomatologii*, №10 (60), 1997, Special Issue, pp 43-44, 80-81).

There is known medication used in various forms, in the form of tablet inclusively. It contains surface-active components: sulfanate olefins, components of abrasive action like sodium methaphosphate or calcium phosphate while fluorides may be added into formulation as well. (GB No1172904 IPC A61K7/16, 1969).

Prophylactic effect of this medication is grounded on a well-known fluor action, focused on enamel and osseous tissue strengthening. Fluor is more effective with associated sufficient content of calcium and vitamins whereas it does not provide their ingress since calcium phosphate digests badly. The known medication does not secure integrated effect aimed at treatment and prophylaxis of dental and periodontium diseases.

There is known tablet for oral application intended for dental deposit reduction, containing dry powder of seaweed *Ascophyllum nodosum* (RU C2 No2275218, IPC 8 A61Q 11/00, 2006).

This drug is administered to patients suffering from constant formation of dental calculi. Treatment course takes a month. There are administered 2-4 tablets a day. The drug ensures bacterial and calculi elimination and for this reason it serves as a means of prophylaxis of stomatological diseases, caries in particular.

However the known medication does not involve components aimed at prophylaxis of a number of oral diseases. Notwithstanding *Ascophyllum nodosum* is one of the most widespread seaweeds it is not present in traditional human diet.

### **Substance of invention**

The major focus of the present invention is on elaboration of complex formulation in the form of tablet of easy-digestible mineral components, vitamins, microelements intended to make them act as synergists ensuring either local or systemic

effect by ingress of required substances in optimal quantities for the sake of treatment and prophylaxis of oral diseases and foremost caries and non-carious teeth affections.

The given task is being accomplished in the following way. Tablet for prophylaxis and treatment of teeth and periodontium diseases involves following components at a ratio (wt %):

	Magnesium sulfate or magnesium chloride	
	or magnesium lactate or magnesium oxalate	3.26-5.26
	Pyridoxine hydrochloride	0.060-0.074
	Thiamin mononitrate	0.50-0.062
10	Calcium glycerophosphate	30.0-38.9
	Ground laminaria thallus	
	or dried laminaria aqueous extract	1.1-2.2
	Stevioside	0.3-0.9
	Sorbite	10.0-25.0
15	Xylite	10.0-25.0
	Auxiliary components	15.62-45.42

Therapeutic and prophylactic effect of the drug for treatment and prophylaxis of oral diseases is entailed by a combined influence of pyridoxine hydrochloride, thiamin mononitrate, calcium glycerophosphate, laminaria thallus, booster dose of magnesium sulfate, sorbite and xylitol. The drug ensures increase of body functional reserves, enforcing physiological process of teeth tissues mineralization.

Calcium glycerophosphate penetrates easily into mineralized tissues and foremost into teeth and bones that is why in given formulation it is a source of calcium and phosphor for teeth and tissues of periodontium therefore enforcing mineralization processes and increasing anti-carious effect of formulation as a whole. Besides calcium glycerophosphate is a regulator of calcium and phosphor metabolism, endowed with bracing and roborant effect by heightening metabolic processes in human body.

Pyridoxine hydrochloride (vitamin B<sub>6</sub>) is an active participator in metabolism relevant for normal functioning of central and peripheral nervous system. Penetrating into body it phosphorilates, transforms into pyridoxole-5- phosphate and forms enzymes which decarboxilate and transaminate aminoacids, i.e. it plays active part in most important life processes. It takes part in metabolism of essential aminoacids, such as

methionine tryptophane, cysteine, glutamic and other aminoacids. It plays important role in histamine metabolism, contributes to normalization of lipidic and according to some data, carbohydrate metabolism, heightening prophylactic effect of formulation as a whole. Vitamin B<sub>6</sub> participates directly in maintaining of structure and bone solidity.

5           Thiamin mononitrate (vitamin B<sub>1</sub>) on penetrating into body transforms into co-fermentative forms of fermentative systems which play relevant part in carbohydrate and fats metabolism and in nerve impulse conduction in synapse as well. All processes of intestinal absorption carried out by mechanism of active energy-dependend transport; increase and renewal of intestinal enterocytes and osseous cells; synthesis of collagen  
10 and other proteins of osseous tissue require constant flow of energy which is drawn from processes of biological oxidation. Vitamin B<sub>1</sub> is indispensable participator in such processes.

          Ground laminaria thallus (seaweed) or dried laminaria aqueous extract contain complex of most important microelements (titanium, nickel, cuprum, argentum, iodine,  
15 zinc, ferrum etc.), macroelements (phosphor, calcium, magnesium etc.), aminoacids including all essential ones like chlorophyll, carotinoids, vitamins; polysaccharides like alginic acid, fucoidane, laminarin. If the components indicated presented in one product they perform the function of active synergists. In confirmation to scientific research there are no collateral phenomena observed in seaweed use which is traditional human  
20 food product. The basic advantage of laminaria is iodine content which digests better and improves protein, phosphor, calcium, ferrum assimilation, activates fermentative systems as well. Moreover laminaria eliminates vitamin-mineral deficiency and brings to normal nervous, cardio-vascular and respiratory systems and builds up immune system, fosters normalization of thyroid function. In whole it ensures physiological  
25 body homeostasis.

          Magnesium salt, magnesium sulfate, magnesium chloride listed among inorganic magnesium salts or magnesium lactate, magnesium oxalate from the list of organic magnesium salts is added into formulation as magnesium source relevant for regulation of many physiological metabolism processes including intra- and  
30 extracellular balance of potassium, magnesium, sodium and calcium in a body on cellular level that improves prophylactic effect of formulation as a whole. As well as calcium, magnesium forms mineral base of osseous tissue. It plays important part in

osteogenesis and can influence directly osseous cells function, vitamin D and calcium metabolism, formation and growth of oxyapatite crystals.

Stevioside (stevia herb extract) is applied due to content of active antioxidants in this extract (such as flavonoids, hydroxyl-proline acids, cumarins) and also some  
 5 potassium, magnesium, zinc, selenium, ferrum, calcium and sodium that as a whole enhance prophylactic effect of formulation.

Xylite, sorbite have bacteriostatic effect inhibiting growth of dentogingival plaque and streptococci metabolism, contributes to pH saliva level thereby securing favourable environment for enamel mineralization especially combined with complex of  
 10 mineral and other bioactive substances. It is matter of high priority since formulation is intended for systemic and local (dental) effect.

In the preferred option of invention realization tablet involves following auxiliary components at a ratio, wt %:

	Lactose	0.12-0.37
15	Cocoa-powder	0.15-0.35
	Calcium phosphate	2.0-5.0
	Food flavors	0.3-0.9
	Food dye	0.05-0.30
	Banding component	12.0-35.0
20	Lubricating component	1.0-3.5

Lactose, cocoa-powder, food flavors, banding and lubricating auxiliary components ensure process of formulation pelletizing and its pleasing flavor. Calcium phosphate serves as a filler. As a banding component necessary for tablet formation it is preferable to use soya or milk protein or fructose.

25 As a lubricating component relevant for flowability improvement and adhesiveness reduction in tablets pressing, it is preferable to use magnesium stearate however there may be used calcium stearate or stearic acid.

Proposed formulation in the form of lozenge is devised for systemic and local (on teeth directly) prophylactic action that is why some components perform two  
 30 functions; of locally-acting agent and filler. Among such components there are listed sorbite, xylite, stevioside.

### Realization of invention

In table 1 there are listed average readings of active components content in tablets with mass of 1000 mg. according to their optimal ingress into body.

Table 1

No	Names of components	Content in mg		% of ACL <sup>**</sup> ) in 3 tablets
		In one tablet	In 3 tablets	
1	Calcium glycerophosphate including	349,2	1047,6	
	- calcium	66,7	200,1	20
	- phosphor	51,3	153,9	19
2	Magnesium sulfate including	42,6	127,8	
	- magnesium	4,2	12,6	3,2
3	Laminaria thallus including	17	51	
	- iodine	0,017	0,051	34
4	Pyridoxine hydrochloride (B6)	0,667	2	100
5	Thiamin mononitrate (B1)	0,567	1,7	100
6	Filler and other components <sup>*)</sup>	589,966		
7	Total	1000		

5

<sup>\*)</sup> - as a filler there are used auxiliary components like sorbite, xylite, soya protein, stevioside, cocoa-powder, magnesium stearate, calcium phosphate.

<sup>\*\*)</sup> - ACL – adequate consumption level; recommended levels of consumption of food and bioactive substances.

10

In table 2 there are illustrated specific examples of tablet formulations prepared in compliance with the invention. Use of other magnesium salts listed among those corresponding to the invention, particularly magnesium chloride or magnesium lactate or magnesium oxalate instead of magnesium sulfate indicated in the examples, yields to similar results and does not tell on effectiveness of medication.

In accordance with method of formulation preparation in the form of lozenge, in example 1 there is demonstrated maximal dosage of components.

In example 2, formulation in the form of lozenge is similar to example 1 but components are represented at optimal (medial) ratio.

5 In example 3 there are represented data of formulation in the form of lozenge with minimal content of components.

Lozenge preparation is carried out according to usual tablet technique.

First there is obtained mass for pelletizing by porphyρίζing, dosing, sorting, mixing of components, then it is subjected to wet granulation, powdering and mixing.

10

Table 2

Components of formulation	Example 1 (wt %)	Example 2 (wt %)	Example 3 (wt %)
Magnesium sulfate	5.26	4.26	3.26
Pyridoxine hydrochloride	0.074	0.067	0.060
15 Thiamin mononitrate	0.062	0.057	0.052
Calcium glycerophosphate	38.90	34.92	30.92
Laminaria thallus	2.2	1.7	1.5
Stevioside	0.9	0.5	0.3
Sorbite	10.0	17.5	23.0
20 Xylite	10.0	17.5	23.0
Lactose	0.37	0.25	0.12
Magnesium stearate	3.5	2.5	1.0
Calcium phosphate (calcium phosphate)	5.0	3.5	2.0
Soya protein	23.38	16.4	13.39
25 Flavors	0.31	0.6	0.9
Food additives	0.05	0.25	0.50

Later the prepared mass is pelletized, tablets are dedusted and packed.

Mustered-out tablets are directed to recycling.

30

Described technique does not undergo any changes if there were used other components corresponding to the invention but not indicated in table 2; neither does it in case of application of various auxiliary components corresponding to the invention.



Tablets should be resolved, therefore a part of active components is actively absorbed through mucous membrane and other part while in a mouth will have local remineralizing influence.

It is prescribed to use 2-3 tablets during the day after teeth brushing. This course takes 1-1.5 month. Second course will take place in 5-6 months.

Tablets are applied in order to improve dental tissues mineralization and for prophylaxis and treatment of dental hypersensitivity. It is illustrative that tablets invented are efficient in its elimination.

22 volunteers agreed to participate in the studies. There were studied and analyzed processes of enamel remineralization on the ground of determination of index of teeth hypersensitivity prevalence (ITHP), intensity (ITHI), hygiene index, PMA and Schiller-Pisarev test.

In table 3 there are shown hygiene index and dental hypersensitivity readings obtained during the survey.

15

Table 3

Fedorov-Volodkina hygiene index (points)		ITHP(%)		ITHI (points)		Green-Vermilon hygiene index (points)		Index PMA (%)		Schiller-Pisarev positive test (%)	
Before application	3.25 ± 0.09	Before application	31.5 ± 2.5	Before application	1.83 ± 0.05	Before application	2.89 ± 0.09	Before application	33.2 ± 1.5	Before application	92.0 ± 8.8
After application	1.60 ± 0.08	After application	9.7 ± 0.8	After application	1.25 ± 0.04	After application	1.62 ± 0.08	After application	12.03 ± 0.8	After application	11.0 ± 5.0

Figures represented in table 3 show a sharp change in indices of hygiene, prevalence and intensity that testifies to enhancing of teeth remineralization. The difference is significant ( $p < 0.05$ ).

5 Alongside substantial improvement of periodontium state has been observed according to all objective indices (index  $\pm$ PMA and Schiller-Pisarev test). The difference is significant ( $p < 0.01$ ).

Hereafter there are shown examples of application of tablets for prophylaxis and treatment of dental and periodontium diseases in medical practice.

#### Example 1

10 Patient X, 39 years of age, complained on high teeth sensitivity, sore and gingival hemorrhage, offensive breath. Up to this complaint she had used only fluor-containing tooth-pastes for regular hygiene. Here are objective results of the investigation:

Hygiene index – 2.75 points;

15 Schiller-Pisarev test – positive;

PMA index – 38.6%;

ITHP – 49.8%

ITHI – 2.35 points.

20 On teeth scaling periodontium tissues and teeth were treated according to traditional method, rinsed by solution of hydrogen peroxide and potassium permanganate.

Then there were given teeth care instructions to the patient since proposed formulation in the form of lozenge with optimal component content (example 2 in table 2) is intended for systemic and local effect on periodontium tissues due to physiological  
25 process of enamel and dentin remineralization. Besides there was administered other tooth-paste because dental deposit elimination aids to enhance local effect of formulation.

30 On 32 days of new formulation application the patient had no complaints. There was marked next to complete disappearance of gingival hemorrhage and gingivitis and offensive breath as well. Teeth hypersensitivity reduced considerably.

Here are objective results of the investigation:

Hygiene index – 1.65 points;

Schiller-Pisarev test – weak positive;

PMA index – 12.3%;

ITHP – 23.7%;

ITHI – 1.58 points.

5 On 62 days of the survey therapeutic effect of medication became more pronounced. There were no complaints.

Hygiene index – 1.45 points;

Schiller-Pisarev test -negative;

PMA index dropped to 8.5%;

10 ITHP – 17.6%;

ITHI – 1.2 points.

Teeth hypersensitivity practically disappeared.

Example 2

15 Patient Y, 28 years of age, complained on oversensitivity of almost all teeth, frequent gingival hemorrhage and edema, itch in oral cavity tissues.

According to objective results:

Hygiene index – 3.2 points;

Schiller-Pisarev test -positive;

PMA index – 38.7%;

20 ITHP – 65.6 %;

ITHI – 2.35 points.

25 On scaling teeth and periodontium underwent antiseptic preparation. There was tooth-paste recommended and administered medication for three-time application prepared in accordance with the invention at a minimal content of active components (example 3 table 2).

On 33 days of tablets application the patient felt notable improvement; recorded gingival hemorrhage and gingivitis reduction.

Hygiene index dropped to 1.6 points;

Schiller-Pisarev test became weak positive;

30 ITHP – 42.5 %;

ITHI – 1.65 points.

Teeth hypersensitivity weakened.

On 65 days of medication application indices of teeth state improvement became more evident.

Hygiene index improved to 1.5 points;

Schiller-Pisarev test – negative. Inflammation qualitative signs were not elicited;

5 PMA index dropped to 17.2%;

ITHP – 14.6 %;

ITHI – 1.4 points.

Dentin hypersensitivity practically disappeared.

Example 3

10 Patient Z, 39 years of age, complained on expressed hypersensitivity of almost all teeth after meals, cold drinks and sweets. Besides there were marked hemorrhage and gingivitis.

According to objective results:

Hygiene index -3.5 points;

15 Schiller-Pisarev test –positive;

PMA index – 38.6%;

ITHP – 63.6 %;

ITHI – 2.8 points.

20 On teeth scaling and standard teeth and periodontium tissues antiseptic treatment (with 3% solution of hydrogen peroxide and rose solution of potassium permanganate) there was tooth paste recommended and administered invented tablets (their formulation is illustrated in example 2, table 2).

In 35 days it was recorded substantial reduction of gingival hemorrhage and edema, teeth hypersensitivity to various stimuli (thermal, chemical and to touch).

25 Hygiene index -1.9 points;

Schiller-Pisarev test – weak positive;

PMA index – 18.3 %;

ITHP – 22.8 %;

ITHI – 1.65 points.

30 In 65 days the survey revealed disappearance of gingival hemorrhage and edema and next to complete absence of teeth hypersensitivity.

Hygiene index -1.5 points;

Schiller-Pisarev test –negative;

PMA index – 11.4 %;

ITHP – 13.6%;

ITHI – 1.3 points.

5            Thus the examples illustrated point to positive influence of medication on teeth and mouth cavity tissues while at optimal and medial balance of components results of application of new formulation in the form of chewing tablets have been better.

10            Use of medication for prophylaxis of dental and periodontium diseases has made it possible to enhance tissues mineralization, eliminate or reduce dentin hypersensitivity according to objective ITHP and ITHI figures; along with gingivitis and gingival hemorrhage according to PMA index and Schiller-Pisarev test dynamics. It was caused by hypersensitivity elimination and teeth-brushing improvement.

15            The conducted studies render it possible to recommend this formulation for caries prophylaxis. Application course duration depends on caries intensity. If there formed one cavity in a year, one-month course is recommended twice a year. If there formed two or more cavities in a year, two month courses are recommended with four month intervals between them.

### Claims

1. Tablet for prophylaxis and treatment of dental and periodontium diseases containing following components at a ratio, wt %:

5	Magnesium sulfate or magnesium chloride or magnesium lactate or magnesium oxalate	3.26-5.26
	Pyridoxine hydrochloride	0.060-0.074
	Thiamin mononitrate	0.50-0.062
	Calcium glycerophosphate	30.0-38.9
10	Ground laminaria thallus or dried laminaria aqueous extract	1.1-2.2
	Stevioside	0.3-0.9
	Sorbite	10.0-25.0
	Xylite	10.0-25.0
	Auxiliary components	15.62-45.42

15

2. Tablet according to point 1 contains following auxiliary components at a ratio, wt %:

	Lactose	0.12-0.37
	Cocoa-powder	0.15-0.35
20	Calcium phosphate	2.0-5.0
	Food flavors	0.3-0.9
	Food dye	0.05-0.30
	Banding component	12.0-35.0
	Lubricating component	1.0-3.5

25

3. Tablet according to point 2 differs in fact that auxiliary component is soya or milk protein or fructose.

4. Tablet according to point 2 differs in fact that lubricating auxiliary component is stearic acid or magnesium stearate or calcium stearate.

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# INTERNATIONAL SEARCH REPORT

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**A. CLASSIFICATION OF SUBJECT MATTER**

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*A61P 1/02 (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 36/03, 33/06, 31/4415, 31/51, 31/7028, 9/20, A61P 1/02, A61Q 11/00

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)  
USPTO, PAJ, Esp@cenet, Enterez PubMed, JOPAL, EAPO

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	RU 2248787 C2 (DZE PROKTER END GEMBL KOMPANI) 27.03.2005, p.p.13-15	1-4
A	SU 1644963 A1 (LENINGRADSKY GOSUDARSTVENNIY INSTITUT USOVERSHENSTVOVANIYA VRACHEI et al.) 30.04.1991	1-4
A	RU 2233651 C2 (DZE PROKTER END GEMBL KOMPANI) 10.08.2004	1-4
A	CN 1209314 A (HAMULATI WUFUER SILAFU AIBAI) 03.03.1999, abstract	1-4
A	RU 2275218 C2 (SDK SVIDENKEA AB) 27.04.2006	1-4

Further documents are listed in the continuation of Box C.  See patent family annex.

\* Special categories of cited documents:

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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</p> <p>"&amp;" document member of the same patent family</p>
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