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NANOCRYSTAL CALCIUM PHOSPHATIC MATERIALS INTENDED FOR USE IN THE QUALITY OF FILTERS FOR PROTECTION FROM ULTRAVIOLET RADIATION

The prospects article considers materials used as inorganic filters in sunscreens and moisturizers existing on the market, lipsticks and powders. The possibility of using synthetic nanocrystalline materials of calcium phosphate composition in cosmetic sun protection products for replacing inorganic filters of titanium dioxide and zinc oxide, traditionally used as filters for ultraviolet radiation, has been determined. It has been shown that ecological pure synthetic nanocrystalline $Ca_{10}(PO_4)_6(OH)_2$ powders can be obtained using the methods of "green chemistry" from solutions of $Ca(OH)_2$ and $H_3(PO_4)_2$ grades of "chemically pure" and "analytically pure" The optimal ratios of the initial components and heat treatment regimes are determined, which ensure the production of a powder with a crystal size of 25 – 50 nm at a Ca/P ratio of 1,67. In the heat treatment of powders (after aging) a coarse-grained crystalline structure is formed, the particle size rises to 75 nm. The skin-irritating and skin-resorptive properties of the developed materials were studied on warm-blooded animals – guinea pigs of the light mask and white laboratory rats on the change in the intensity of biochemiluminescence of whole animal blood and on the changes in the biochemical parameters of blood serum constants of experimental and control animals. When carrying out a full complex of toxicological and hygienic tests in vivo, it is established that the obtained materials do not possess skin-rending properties and are biocompatible with the tissues of the body.

***Keywords**: synthetic sunscreens, hydroxyapatite, titanium dioxide, inorganic filters, skin irritant, skin-resorbing properties.*

Entrance. Analysis of the recent research and publications

In recent years there has been a tendency for the introduction of innovative technologies and modern functional materials developed for restorative surgery, cosmetology and dermatology [1 – 3]. Here they are used as ingredients of various creams, moisturizers, powder and toothpastes. Today nanomaterials are used in many cosmetic products, including nanocrystals in sunscreens and moisturizers, special toothpastes, powders, lipsticks and oral care products. According to the European Commission, more than 10 % of cosmetic products contain nanoparticles [4 – 7].

Nanotechnology is becoming the determining factor in the development of aesthetic cosmetology and dermatology.

In cosmetic medicine today there are two main directions of using nanotechnology. The first is the application of nanoparticles as UV filters, the second is the targeted delivery of cosmetic products [8 – 12]. Over the past 20 years, the views on the influence of the Sun on human health have changed greatly. Now the pronounced tan is no longer considered a sign of good health or life's success. The growth of oncological diseases made doctors recommend to the population to protect the skin from the aggressive effects of excess ultraviolet radiation by means containing UV filters. These are blocking substances containing light-protective substances in the form of fine-grained inorganic or organic particles. The need for such tools is great. The volume of the market of cosmetics and the whole post-Soviet space is significant. Today, its saturation is less than 20 %, and a steady growth of 10 % per year is expected.

At present, the number of people using sunscreens is increasing, but the incidence of skin cancer also increases. The statistics of oncological skin diseases in the world are plagued: on the first place is the countries with white population and developed beach tourism. It is because 2 / 3 of sunscreens contain potentially harmful ingredients.

All sunscreens contain UV sorbents – substances that reduce the amount of ultraviolet radiation that affects the skin.

For UV protection, nanoparticles of 300 nm (Rohm and Haas) styrene and acrylate copolymers, SiO_2 nanoparticles and benzoyl peroxide nanoparticles in SiO_2 coatings ("Sol-gel-Technologies"), other organic filters of the new generation ("Ciba Specialty") are used for protection against ultraviolet radiation.

But most often for these purposes, inorganic particles ZnO and TiO_2 are used. While earlier UV-sorbents contained large insoluble particles of these compounds, giving a white effect on the surface of the skin, today many manufacturers switch from their use to nanoparticles ZnO and TiO_2. This makes the product more transparent, less slippery and avoids whitening of the skin, especially when TiO_2 is used. But now when transitioning to nanometer range, nanoparticles ZnO and TiO_2 are quickly absorbed and can penetrate into the upper layers of the skin. And since both of these compounds are foreign to the organism, their use raises a well-founded fear. In connection with this, it is promising to use nanocrystalline calcium phosphate materials of apatite composition similar to the composition of the bone tissue, as filters of UV radiation [2, 3]. The peculiarity of these materials is the presence of both themselves and their metabolites in the human body, as well as high biocompatibility with living tissues [13].

$Ca_{10}(PO_4)_6(OH)_2$ is also promising as a filler, stabilizer and emulsifier for many cosmetic products, and in particular, components of powder, lipsticks and creams that improve the structure of the skin (which it compresses and restores). Synthetic hydroxylapatite under laboratory conditions is obtained by chemical methods: from solutions, solid-phase and hydrothermal. In practice, large amounts of $Ca_{10}(PO_4)_6(OH)_2$ are more expedient and economical to obtain from solutions. But the use of nitrates for this purpose leads to contamination of the final product, requires additional technological treatment methods with not always guaranteed result. For all dissolved methods, a variety of variable factors (reaction temperature, concentration of starting materials, pH of the solution, duration of the process, order and speed of mixing, aging time, etc.) are characteristic. This impedes the stable reproducibility of the results [14] and often results in the production of powders with different specific surface, size and agglomeration of crystals, morphology, stoichiometry and degree of crystallinity (i.e. leads to the production of ceramic materials with unsatisfactory properties). In addition, when using many of the dissolved methods (especially when leaving laboratory volumes), significant volumes of waste are produced in the form of chemically aggressive solutions, which is not environmentally friendly. At the same time, practically all solvent methods are too laborious and expensive.

As for numerous publications and patents devoted to the methods of obtaining hydroxylapatite in ceramics, their developers prefer not to specify the technical features and technological subtleties of its receipt (this is known as "know-how" applicants). Publications are reduced, at best, to a superficial description, and at worst – to the banal advertisement of their products. In most cases, this makes it impossible to reproduce the technology, as well as to compare the claimed materials.

In this regard, it seems promising to obtain the environmentally safe nano-sized $Ca_{10}(PO_4)_6(OH)_2$ powders by "green chemistry" methods intended to replace ZnO and TiO_2 based ultraviolet filters as sunscreens.

Problem statement

It is known that the effectiveness of hydroxylapatite $Ca_{10}(PO_4)_6(OH)_2$ when it is used as a light protective filter in cosmetics more than 9 % exceeds the efficiency of the use of traditionally fine particles ZnO and TiO_2 for these purposes.

The structure of GA allows different kinds of substitution of some elements by others. For example, when replacing hydroxyl groups, the OH-ions of fluorine F-have a stabilizing effect on the structure of the material and, with complete substitution, the solubility decreases by an order of magnitude [15]. Thus, the use of fluorapatite supplements should improve its stability in contact with the chemically aggressive environment of the organism (due to the F-ions).

The nanocrycrystalline hydroxyapatite synthesized by us, intended for use in surgery of the skeleton by the methods previously given [1], is a synthetic analogue of the mineral component of bone tissue. It is able to regulate the metabolism of calcium and phosphorus in the body. Its main mineral is $Ca_{10}(PO_4)_6(OH)_2$, the Ca/P ratio is stoichiometric and equal 1,67. In its structure it is crystalline with the particle size in the nanometer range.

It should be noted that the potential risk of intravenous use of sols based on nano-dispersed powders of hydroxyl-apatite (as fillers to replenish lost muscle tissue) does not extend to the use of these materials in cosmetic sunscreens, since particles of $Ca_{10}(PO_4)_6(OH)_2$ in deep layers of the skin and blood flow do not penetrate.

The study of the effect of materials on the skin and mucous membranes is mandatory in the conduct of sanitary toxicological studies of chemicals, preparations and cosmetic materials. It has a definite significance in connection with the diverse nature of the local action of substances when used in both the various fields of medicine and cosmetology.

The purpose of this work is to conduct a study on obtaining green chemistry of environmentally friendly nano-sized $Ca_{10}(PO_4)_6(OH)_2$ powders potentially suitable for use as UV filters in the composition of sunscreens and studying their properties. To achieve the goal, the following tasks had to be solved:

To synthesize environmentally friendly nano-sized $Ca_{10}(PO_4)_6(OH)_2$ and $Ca_{10}(PO_4)_6F_2$ powders, to study their microstructure and properties:

1. Determine the optimal content of the components.
2. Determine whether the obtained materials have skin-resorptive properties.
3. Determine whether the resulting materials have an irritant effect on the skin and mucous membranes.
4. To conduct a full complex of toxicological and hygienic tests of developed materials on warm-blooded animals.

Experimental part

In the work, the following reagents were used: erythophosphoric acid H_3PO_4, CaF_2, $Ca(OH)_2$ of the marks of "chemically pure" and "analytically pure". $Ca_{10}(PO_4)_6(OH)_2$ was prepared from solutions of $Ca(OH)_2$ and H_3PO_4 in distilled water by mixing them for 8 hours and holding them for 170 hours at room temperature for aging, ensuring the ratio of Ca ions and phosphate ions in solution $n(Ca_2^+)/m(PO_4^-) = 1,67$. The product ob-tained was filtered and the precipitate was dried at 80 °C. For the synthesis of $Ca_{10}(PO_4)_6F_2$, $Ca_3(PO_4)_2$ was presynthesized (by treating the tableted blends at a temperature of 1150 – 1250 °C with annealing for 2 hours and intermediate chopping with a multistage climb temperature at a rate of 120 – 150 °C per hour). The fluorapatite $Ca_{10}(PO_4)_6F_2$ was synthesized from CaF_2 and $Ca_3(PO_4)2$ by firing in the temperature range 1200 – 1250 °C with annealing for 3 hours followed by grinding. The resulting fluorapatite was then milled in a ball mill to particles of the required size.

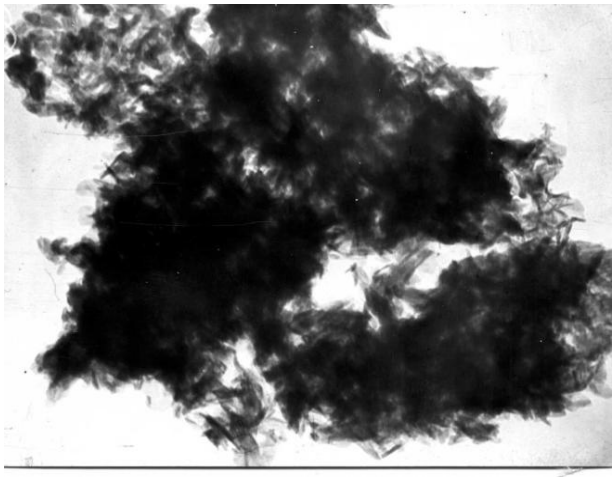
The firing was carried out in a chamber furnace in an airy atmosphere in corundum crucibles. Temperature control was carried out using platinum-rhodium thermocouples PPR-10rh, 90-Pt. To deter-mine the optimal, we selected various component ratios.

According to the analyzes, nano-crycrystalline hydroxyapatite synthesized by us, intended for use in surgery of the skeleton [18], is a synthetic analogue of the mineral component of bone tissue. It is able to regulate the metabolism of calcium and phosphorus in the body. Its main mineral is $Ca_{10}(PO_4)_6(OH)_2$, the Ca / P ratio is stoichiometric and equal 1,67. According to its structure, it is crystalline with a particle size in the nanometer range: from 25 to 50 nm, with a degree of crystallinity over 96 %, a mass fraction of calcium of 40,82 %, and a mass fraction of phosphorus of 15,8 %. In the heat treatment of powders (after aging) a coarse-grained crystalline structure is formed, the particle size rises to 75 nm.

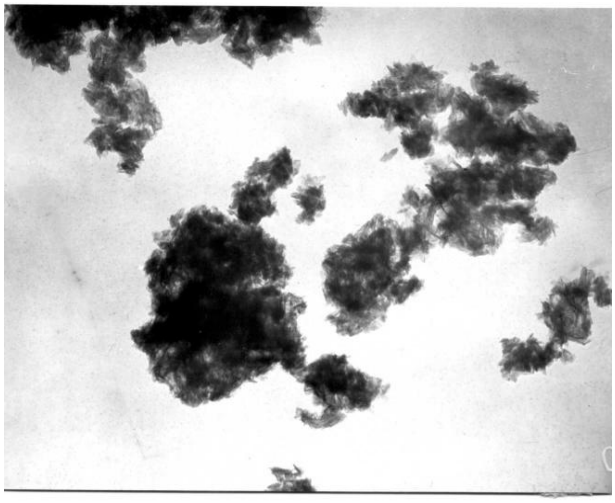
X-ray diffraction analysis was carried out on a diffractometer on the DRON-2.0 installation using the standard procedure. X-ray of samples of drugs showed that all reflections on the X-ray images correspond to pure $Ca_{10}(PO_4)_6(OH)_2$ and $Ca_{10}(PO_4)_6F_2$, which were identified by comparison with the ASTM data. Chemical interaction between them does not occur and new chemical compounds do not appear. Synthesized hydroxyapatite and fluorapatite practically do not contain impurities of other calcium phosphates ($Ca_2P_2O_7$, $Ca_3(PO_4)_2$ and etc.), as well as heavy metals.

The microstructure of the obtained materials in their synthesis process was investigated using Carl Zeiss scanning electron microscope, Germany. In the pictures 1 and 2 are shown the electron microscopic photos of the microstructure of nanocrystalline powders of $Ca_{10}(PO_4)_6(OH)_2$ after 1 and 5 days of aging.

In the picture 3 is shown the electron microscopic photo of the microstructure of nanocrystalline powders of $Ca_{10}(PO_4)_6(OH)_2$. after drying at 80°C.



Pic. 1. Electron microscopic photograph of the $Ca_{10}(PO_4)_6(OH)_2$ microstructure after aging for 1 day, (× 70000)

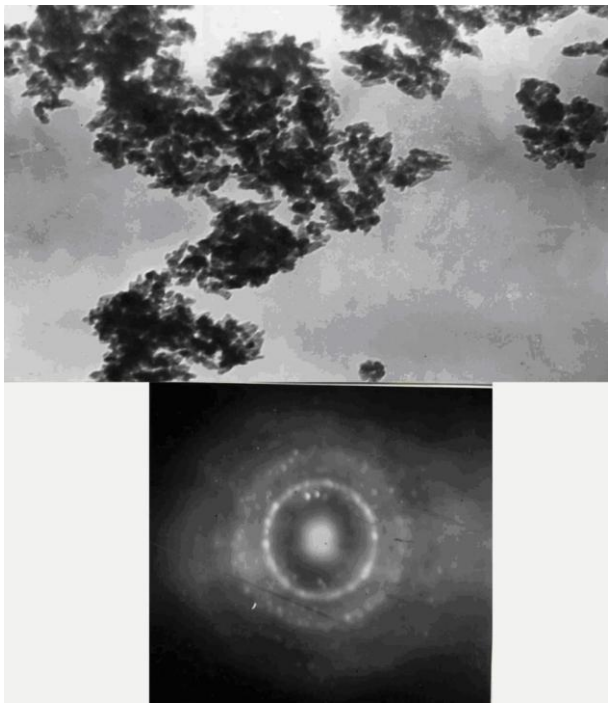


Pic. 2. Electron microscopic photograph of the $Ca_{10}(PO_4)_6(OH)_2$ microstructure after aging for 3 day, (× 49000).

The significant influence of the temperature of synthesis on the morphology (from needle to spherical) crystallizing particles of nanocrystalline powders has been established.

The study of the irritant action on mucous membranes of materials that are based on hydroxylapatite was performed on guinea pigs. Extracting materials after2 hours of boiling in water and the clean powders themselves in dilution with sunflower oil in a ratio of 1 : 2 were studied, which in the amount of 2 to 3 drops were introduced into the conjunctive sac of the right eye of the guinea pig.

The left eye served as a control. After instillation, the animals remained calm, there was a slight lacrimation. Injection of vessels of sclera and conjunctiva was practically absent.



Pic. 3. Electron microscopic photograph of microstructure of nanocrystalline $Ca_{10}(PO_4)_6(OH)_2$ powder after drying at 80 °C, (× 28500).

This made it possible to conclude that the hydroxyapatite based material does not exert an irritating effect on the mucous membranes of the eye.

The skin-irritating properties of the developed materials were studied for two weeks on warm-blooded animals – guinea pigs of light weight. For this, wool on a 5 × 5 cm area was removed on both sides of the guinea pig. On the right side, wet applications of the investigated materials were applied in the amount of 200 – 300 mg, and on the left, which served as control, tap water. An estimate of skin-irritant action was carried out in the points on Alekseyeva O. G. [16]. About skin-resorptive action was judged by the change in the intensity of bio-chemiluminescence of whole blood of animals and by alteration of biochemical constants of serum of blood of experimental and control animals (as used by white laboratory rats) according to Vladimirov A. and Archakov A. I. [17, 18].

It was found that neither single, nor repeated applications for 4 hours daily during two weeks did not reveal skin irritant and skin-resorptive action of the materials under investigation. Thus, the obtained results indicate that ceramic materials based on hydroxyapatite do not have skin-resorptive properties and have no irritating effect on the skin and mucous membranes.

The developed materials have passed a complete complex of toxicological and hygienic tests on warm-blooded animals. It was found that they are low-toxic, low-risk substances with weakly cumulative properties. In addition, they do not possess gonadodotoxic, embryotoxic, cytotoxic, mutagenic and teratogenic effects.

The performed researches show that synthesized nanocrystalline powders based on hydroxylapatite can be used in light protection products as inorganic filters of the new generation. Not only do they not have a toxic effect on the body, but they are not foreign to it (as opposed to TiO_2 and ZnO), since it itself $Ca_{10}(PO_4)_6(OH)_2$ and products of its decomposition are always present in the body.

This will allow modern cosmetology to reach a new level of protection against ultraviolet radiation, thus reducing the percentage of skin cancer incidence among the population.

Conclusions

As a result of the research carried out by the classical method from solutions using chemically pure reagents, environmentally friendly nano-size $Ca_{10}(PO_4)_6(OH)_2$ powders with additives of $Ca_{10}(PO_4)_6F_2$ were obtained.

It has been determined that up to 10 % of $Ca_{10}(PO_4)_6F_2$ injections improve the stability of the material when in contact with the chemically aggressive medium of the organism (due to F-ions). It has been determined that the administration of 5,5 % $Ca_{10}(PO_4)_6F_2$ is optimal.

It was established that the obtained materials do not have skin-resorptive properties and have no irritating effect on the skin and mucous membranes.

A complete complex of toxicological and hygienic tests of the developed materials on warm-blooded animals was carried out.

It was established that they are low-toxic, low-hazard substances with poorly expressed cumulative properties; they do not possess gonadotoxic, embryotoxic, cytotoxic, mutagenic and teratogenic effects.

The developed materials are potentially promising for use as ultra-disperse fillers in sunscreen as UV filters.

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НАНОКРИСТАЛІЧНІ КАЛЬЦІЙФОСФАТНІ МАТЕРІАЛИ, ПРИЗНАЧЕНІ ДЛЯ ВИКОРИСТАННЯ У ЯКОСТІ ФІЛЬТРІВ ДЛЯ ЗАХИСТУ ВІД УЛЬТРАФІОЛЕТОВОГО ВИПРОМІНЮВАННЯ

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У статті розглянуті матеріали, що використовуються в якості неорганічних фільтрів для ультрафіолетового випромінювання в існуючих на ринку сонцезахисних і зволожуючих засобах, помадах і пудрах. Визначено можливість застосування синтетичних нанокристалічних матеріалів кальційфосфатного складу в косметичних сонцезахисних продуктах для заміни блокуючих речовин з діоксиду титану та оксиду цинку на більш ефективні порошки апатитного складу, які не є чужорідними для організму, оскільки і $Ca_{10}(PO_4)_6(OH)_2$, і продукти його деструкції завжди присутні в організмі. Показано, що найбільш перспективним є отримання екологічно чистих синтетичних нанокристалічних порошків гідроксилапатиту із застосуванням методів «зеленої хімії» з розчинів з гідроксиду кальцію і ортофосфорної кислоти марок «х. ч.» і «ч. д. а.». Визначено оптимальні співвідношення вихідних компонентів і режими термообробки, що забезпечують отримання порошку з розміром кристалів 25 – 50 нм, основним мінералом якого є $Ca_{10}(PO_4)_6(OH)_2$ зі співвідношенням Ca / P = 1,67. За своєю структурою він є кристалічним з розміром частинок в нанометровому діапазоні; при термообробці формується більш грубозерниста кристалічна структура, розмір часток зростає до 75 мкм. Фторапатит синтезували з попередньо синтезованого $Ca_3(PO_4)_2$ і з CaF_2 випалюванням в температурному діапазоні 1200 – 1250 °С з витримкою протягом 3 годин з подальшим подрібненням в кульовому млині до часток необхідного розміру. Отримані синтетичні гідроксилапатит і фторапатит практично не містять домішок інших кальційфосфатів ($Ca_2P_2O_7$, $Ca_3(PO_4)_2$ і т. і.) і важких металів. Визначено, що введення 10 % $Ca_{10}(PO_4)_6F_2$ покращує стабільність матеріалу при контакті з хімічно агресивним середовищем організму (за рахунок іонів F^-). Визначено, що оптимальним є введення 5 % $Ca_{10}(PO_4)_6F_2$. Дослідження подразнюючої дії нанопорошків на слизові оболонки та їх шкірно-дратівливих властивостей проводили на теплокровних тваринах. Шкірно-резорбтивну дію оцінювали по зміні інтенсивності біохемілюмінісценції цільної крові і по зміні біохімічних констант сироватки крові дослідних і контрольних тварин (білих лабораторних щурів). Встановлено, що ні одноразові, ні повторні аплікації протягом двох тижнів протягом 4 годин щодня не виявили шкірно-подразнюючої та шкірно-резорбтивної дії досліджуваних матеріалів. Проведено повний комплекс токсиколого-гігієнічних випробувань in vivo. Встановлено, розроблені матеріали біосумісні з тканинами організму і відносяться до малотоксичних, малонебезпечних речовин зі слабо вираженими кумулятивними властивостями. Виявлено, що їм не притаманні гонадотоксичний, ембріотоксичний, цитотоксичний, мутагенний і тератогенний ефекти і вони є потенційно перспективними для використання в якості ультрадисперсних наповнювачів, що виконують роль ультрафіолетових фільтрів у складі сонцезахисних засобів.

Ключові слова: *сонцезахисні креми, гідроксиапатит, діоксид титану, неорганічні фільтри, шкірно-подразнююча дія, шкірно-резорбтивна дія*