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## HYDROPHILIC/HYDROPHOBIC WOUND CARE PREPARATION BASED ON THE NANOSCALE SILICA: PHYSICOCHEMICAL AND TECHNOLOGICAL ASPECTS

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Healing of infected ulcers and wounds, particularly in older people, is a serious problem in modern surgery. As a result of many years efforts, we have created an innovative wound care composition that has high absorptive, anti-inflammatory and wound-healing capabilities and are starting the clinical study of it. The composition, which got a trade mark Pathelen<sup>®</sup>, contains nanoscale hydrophilic silica (A-300), hydrophobic silica (Aerosil<sup>®</sup> R972 Pharma) and benzalkonium chloride. This work aimed to develop an optimal pathway of industrial production, as well as methods of quality control of the drug.

The examination of manufacture intermediates and the final product includes bulk density measurement, thermal analysis, IR spectroscopy, chemical methods of identification, adsorption capacity and microbial contamination control.

The pathway of manufacture which consists of mechanochemical immobilization of benzalkonium chloride on hydrophobic silica surface and mixing of obtained semi-product with hydrophilic nanoscale silica is developed. Thus, a technological method is proposed for combining hydrophilic and hydrophobic nanomaterials in one preparation. The final product complies to the elaborated quality parameters. In particular, the bulk density is distributed in a range 50–60 g/L, the adsorption capacity is not less than 140 mg of protein per gram. The absence of pathogenic microorganisms and fungi was demonstrated; the quantity of non-pathogenic microorganisms meets the requirements of the European Pharmacopoeia for products in this category.

The results obtained can be useful for the organization a large-scale production of the proposed drug in future.

**Keywords:** Wound care, adsorption, nanoscale silica, hydrophobic silica, manufacturing process, quality control

### INTRODUCTION

Healing of infected ulcers and wounds, particularly in older people, is a serious problem in modern surgery. Among wounds, diabetic foot is one of the leading disabling chronic complications of diabetes which causes from 40 to 60 % of all non-traumatic amputations across the globe [1, 2]. Clinical practice shows that the treatment of purulent-inflammatory diseases and infected wounds by using only antimicrobial agents does not always lead to the desired result. Misuse of antibiotics contributes to the emergence of resistant (hospital) strains of pathogenic microorganisms, including methicillin-resistant *Staphylococcus aureus*

(MRSA), which is a serious challenge for modern medicine in general [3, 4].

The intensity of the regeneration process and healing of infected ulcers and wounds depends largely on the speed at which they are cleared from the pus and necrotic tissues. For this purpose applique sorption treatment, *i.e.* a method of wound healing in which a sorbent in powder or another form is applied to the wound, can be used. Applique sorption is a kind of sorption detoxification which accelerates wound healing and restores the integrity of the skin and mucous membranes by the removal of microbial cells, bacterial toxins and toxic metabolites of wound fluid and wound cavities in direct contact

with the surface of the sorptive preparation [5, 6]. An important therapeutic factor in the first phase of wound healing is also seen in the dehydration, *i.e.*, absorption of fluid from the wound cavity and surrounding tissues.

As sorption preparations for topical treatment of wounds materials based on activated carbon, various swelling polymers of synthetic and natural origin in form of dressings and sorbents derived from silica and silicon compounds have been proposed.

Among the carbon preparations for wound healing Actisorb Plus (Johnson & Johnson) is particularly well-known, which is an activated carbon fiber coated with colloidal silver. Actisorb Plus has a nonspecific antimicrobial effect due to silver and can absorb pathogenic metabolites that accumulate in the wound contents. The preparation is used primarily for the healing of superficial wounds and skin defects, such as venous ulcers [7]. However, activated carbon having nanometer pore size cannot absorb large protein molecules, which include bacterial toxins and tissue degradation products.

Various wound dressings are designed to keep the wound clean and free from contamination and also to promote wound healing, particularly in chronic wounds where there may be significant tissue loss, *e.g.*: hydrocolloid dressings, hydrogels, alginate dressings and others [8, 9].

Hydrophilic highly dispersed silica (particle size 10–100 nm, specific surface area  $S_{\text{area}} \geq 295 \text{ m}^2/\text{g}$ ) can be used in the first phase of wound healing. Its detoxifying action is due to the capability to absorb pathogenic protein substances (up to 600 mg/g), including microbial enzymes, endo- and exotoxins and microorganisms. Silica surface is covered with hydroxyl groups that can bind water molecules, so it renders a pronounced dehydrating effect on the tissue, which is important for the removal of edema as a part of the inflammatory process. However, silica, due to lack of porous structure, does not absorb low and middle molecular weight toxic metabolites. Nanosized silica does not show direct antimicrobial action, however, it was found that the sensitivity of pathogenic organisms to antibiotics increased in its presence [10].

Also among sorbents, the hydrophobic polymethylsiloxane (PMS) is known that

provides local wound detoxification due to active sorption of pathogens and low and middle molecular metabolites. Wound exudate fluid is “drained” through a capillary net of the powdered sorbent and organic substances are absorbed into its granules. PMS can be used for the applique sorption with antibiotics immobilized on its surface. Examples of such drugs are “Imosgent” and “Gentaxan” in which the PMS surface is modified by gentamicin [11]. However, in the case of hydrophobic materials, the exudate is not absorbed and spreads rapidly under the bandage which promotes skin maceration and activation of the inflammatory process in the wound [12].

Noteworthy is a combination of hydrophilic highly dispersed silica and hydrophobic PMS, providing sorption of a wide range of substances and pathogenic microorganisms in wounds. Through a combination of hydrophilic and hydrophobic sorbents these products can provide clean wounds through a selective sorption and draining effect.

This new approach represents the wound healing compositions “Flotoxan” and “Metroxan” (Ukrainian patents 32088A and 33629, respectively) which include highly dispersed silica and PMS in a mixture with a cationic surface-active substance and antimicrobial agent. These preparations have a controlled dehydrating effect which depends on the ratio “silica/PMS” and sufficient antimicrobial activity, the capability to absorb and to retain proteins, bacteria and their toxins, metabolites of middle molecular weight, thus preventing the resorption of these substances through the wound surface. The effectiveness of these compositions has been proven in many clinical cases in patients with purulent wounds of various etiology, such as abscess, carbuncle, phlegmon, felon, trophic ulcer, burns of various stages, diabetic foot, *etc.*

Advantages of powder nanocompositions in comparison to the soft preparations (ointments, gels, *etc.*) are presented in Table 1.

The next step was to create the similar wound care composition for the common market, in particular for consumers from the European Union (EU). Because PMS is registered as a medicinal substance only in Ukraine, we replaced it with the Silica, hydrophobic colloidal, which is described in the European Pharmacopoeia (Eur. Ph.) [14]. Benzalkonium

chloride (Eur. Ph.) was used as the cationic surfactant. The modified composition, which has got the trademark Pathelen<sup>®</sup>, consists of a) hydrophilic nanoscale silica (Silica, colloidal

anhydrous accordingly to Eur. Ph.); b) hydrophobic silica (Silica, hydrophobic colloidal) and c) benzalkonium chloride.

**Table 1.** Comparison of highly dispersed sorbents and ointments on water-soluble basis in treatment of purulent wounds in the first phase of wound process [13]

Index	Powder sorbents	Ointments
Distribution on the wound surface	Possess high adhesion to the wound surface	Melt at the temperature of body and flow down on the bottom of wound
Adsorption and osmotic properties	Irreversibly absorb proteins, toxins, microorganisms; take in water. Hydrophobic sorbents do not absorb exudation	Do not absorb toxins and microorganisms; are diluted by wound exudation
Pharmacokinetic features	Can act as carriers of immobilized drugs	Promote deep penetration of drugs into the tissues

The aim of this work is to develop the optimal pathway for manufacturing as well as the methods of quality control for newly proposed drug.

#### MATERIALS AND METHODS

To manufacture Pathelen<sup>®</sup> the initial substances listed in Table 2 were used.

Other materials involved in the manufacturing process were distilled water (supplied in bottles) and 96 % ethanol.

The following equipment was used to make the new composite preparation: a ball mill with a steel drum with a volume of 100 L, a ribbon type mixer (volume 150 L, maximum 50 rpm), a drying cabinet with a volume of 300 L (temperature maximum 300 °C), plastic bulk containers (20–100 L volume) for semi-products and final product storage and conventional laboratory equipment for chemical analysis.

**Table 2.** Formulation of nanocomposition that corresponds to the middle dehydrating effect

Ingredient	Content, (m/m %)	Document	Trade mark	Supplier
Silica, colloidal anhydrous	64	Eur. Ph.	A-300	Kalush Test Experimental Plant of ISC, Ukraine
Silica, hydrophobic colloidal	35.9	Eur. Ph.	Aerosil <sup>®</sup> R972 Pharma	Evonik
Benzalkonium chloride	0.1	Eur. Ph.	–	Alfa Aesar

ISC – Institute of Surface Chemistry

Chemical, physicochemical and microbiology methods described in Eur. Ph. were used to ensure quality control of prepared nanocomposition.

Spectral studies in the infrared (IR) and visible (UV/Vis) range were performed with a spectrophotometer Specord M80 (Carl Zeiss

Jena, Germany) and a spectrophotometer Agilent Cary 60, USA), respectively.

A simultaneous study of thermogravimetric and differential thermal properties (TG/DTG/DTA) of initial substances and final product was performed in a static air atmosphere by a derivatograph Q-1500D (Paulik,

Paulik&Erdey, MOM, Hungary) with the computer data registration. The samples (54.3 mg of benzalkonium chloride /  $302 \pm 2$  mg of A-300 or Aerosil R972 or Pathelen®) placed into a corundum crucible were heated at the rate of  $10^\circ\text{C}/\text{min}$  from 20 to  $1000^\circ\text{C}$ .

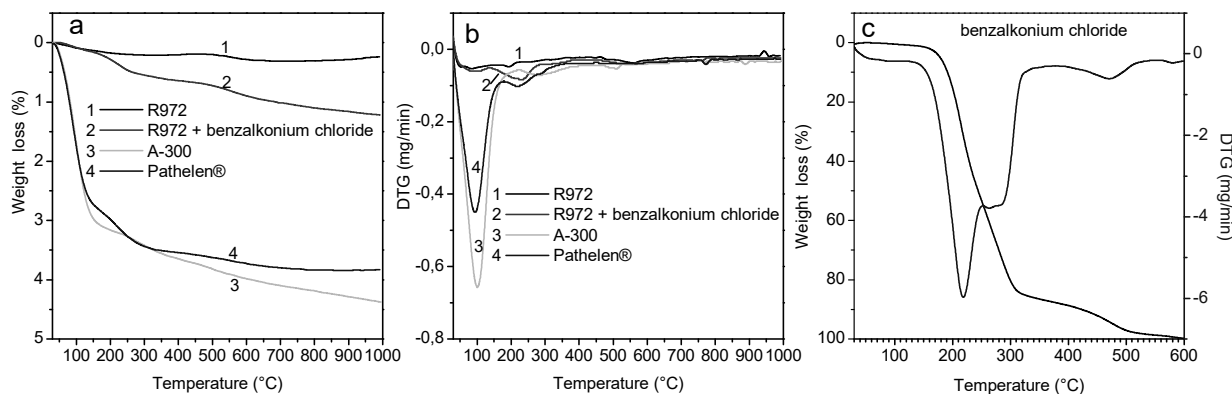
Microbial examination of product was performed according to the methods given in general chapters 2.6.12 and 2.6.13 of the Eur. Ph. The direct plating method using a buffer solution containing neutralizing agents was applied. The need for neutralizing agents is due to the presence in the product of benzalkonium chloride, which may have a certain antimicrobial effect, that, in turn, could affect the final test result. Acceptance criteria for microbiological quality were established in accordance with requirements of the Eur. Ph. (5.1.4) as for non-sterile products for cutaneous use.

## RESULTS AND DISCUSSION

**Technological Part.** Since the preparation contains hydrophobic silica, it is poorly moistened with water. Thus, an aim was to elaborate a way of its hydrophilisation. In this work, a partial hydrophilisation of Aerosil® R972 Pharma was achieved by immobilization on its surface of cationic surfactant benzalkonium chloride. For this purpose, the method of mechanochemical treatment (or mechanochemically initiated immobilization) was used. In this method benzalkonium chloride is adsorbed on the surface of a carrier material [15]. A ball mill serves as the most accessible and productive equipment for this aim. Due to mechanochemical treatment benzalkonium chloride forms a monomolecular layer on the

surface of the highly dispersed carrier material particles to give semi-product “Aerosil R972/benzalkonium chloride”.

The next problem was to obtain a product as free from microorganisms as possible, perfectly – sterile. To study the possibility of using the simplest method – thermal sterilization – we performed TG/DTG analysis of the starting compounds (A-300, Aerosil R972, benzalkonium chloride), the semi-product “Aerosil R972/benzalkonium chloride” and the final product (Pathelen®). The results of these studies are presented in Fig. 1. As seen, in the temperature range from 20 to  $350^\circ\text{C}$ , weight loss is observed on the thermograms of all samples (except Aerosil R972) with maxima at  $\sim 100^\circ\text{C}$  and  $\sim 220^\circ\text{C}$  (Figs. 1 b, c). The first process is related to the loss of adsorbed water and is observed for the initial A-300 and final product (Fig. 1 b, curves 3, 4). The second one reflects the decomposition of benzalkonium chloride (Fig. 1 b, curves 2, 4; Fig. 1 c). It is clearly seen from the DTG curves that water is removed in the temperature range from 20 to  $206^\circ\text{C}$ , which makes it possible to calculate its amount from the TG curves (Fig. 1 a, curves 3, 4). So, the amount of removed water is 3.2 and 3.0 wt. % for initial A-300 and Pathelen®, respectively. Aerosil R972 does not contain water. The decomposition of benzalkonium chloride begins at  $140^\circ\text{C}$  and takes place in several stages with  $T_{\text{max}}$ : 220, 275 and  $480^\circ\text{C}$  (Fig. 1 c). For benzalkonium chloride in Pathelen®, only one  $T_{\text{max}} = 260^\circ\text{C}$  is observed on the DTG curve (Fig. 1 b, curve 4).



**Fig. 1.** TG (a) and DTG (b) curves of Aerosil R972 (1), semi-product “Aerosil R972/benzalkonium chloride” (2), A-300 (3) and final product (4); TG, DTG curves of benzalkonium chloride (c)

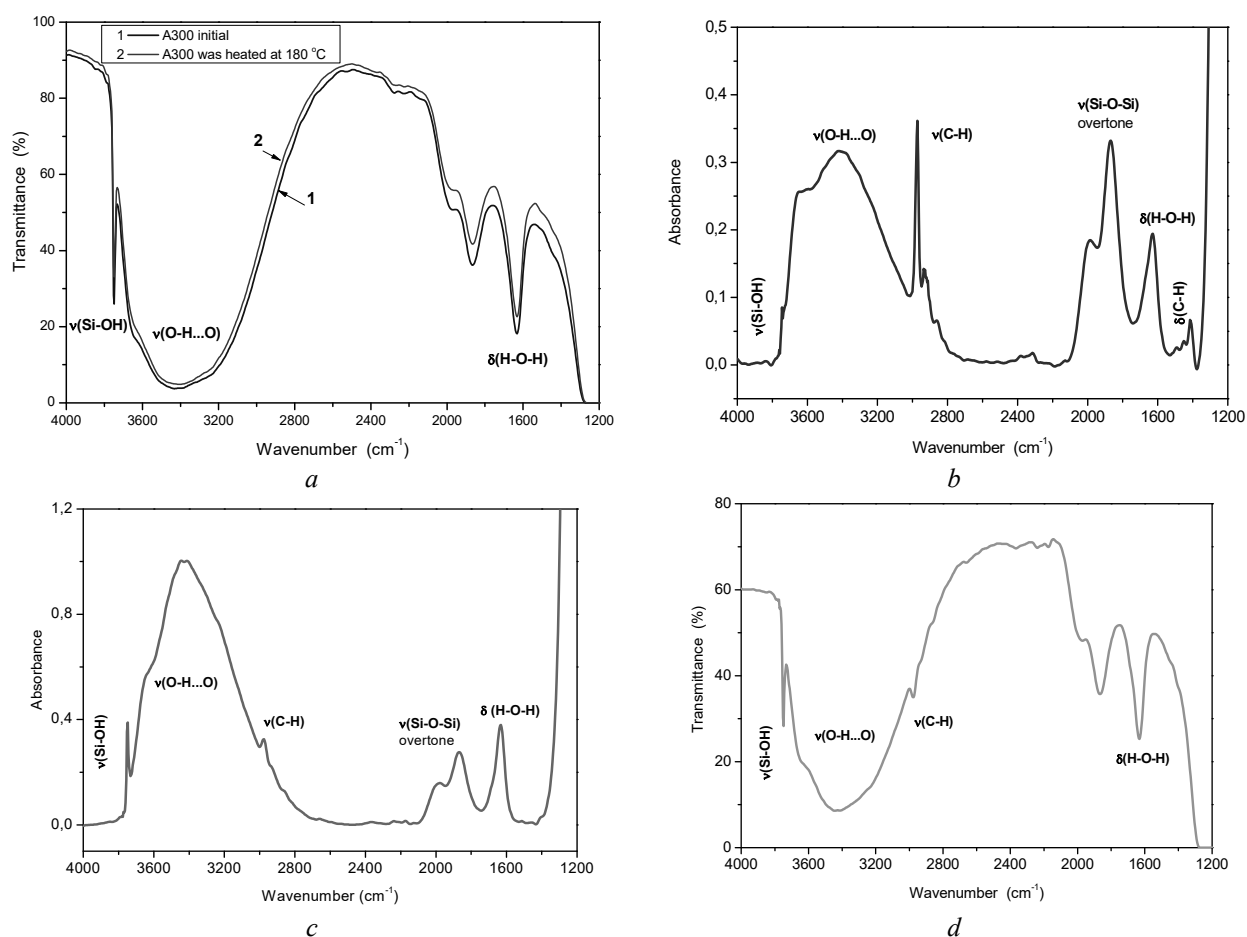
Thus, the above results have shown that for microbial decontamination of the final product thermal sterilization cannot be used, the mildest mode of which provides for exposure at 160 °C. Therefore, we proposed to subject to thermal sterilization only the initial A-300 (180 °C for 1 h) with maximum compliance of microbial purity in the production area.

Below is a brief description of the three stage production process of Pathelen® for a formulation presented in Table 2. This method is protected by the relevant patents [16, 17].

The first stage includes the pre-treating A-300. To get rid of volatile impurities and sterilization, it is enough to heat A-300 at 180 °C

for 60 min. The cooled product is introduced into a sterile plastic container for bulk materials. This stage is constantly performed to accumulate sterilized A-300 “in reserve”.

The IR spectra of initial and heated A-300 are shown at Fig. 2 *a*. The absorption band 3750 cm<sup>-1</sup> corresponds to the oscillations of free silanol groups Si–OH. The broad band with a maximum near 3400 cm<sup>-1</sup> belongs to various forms of sorbed water linked by hydrogen bonds. The band about 1640 cm<sup>-1</sup> corresponds to the deformation oscillations of water molecules. Some weakening of the intensity of a wide band in the range 3600–3100 cm<sup>-1</sup> reflects the removal of physically bound water from the substance.



**Fig. 2.** IR spectra of the initial A-300 and after heating at 180 °C (*a*), semi-product “Aerosil R972/benzalkonium chloride” (*b*) and the final product (*c*, *d*)

The second stage is immobilization of benzalkonium chloride on the Aerosil R972 particles. Approximately 500 mL of a solution of benzalkonium chloride in 96 % ethanol in a ratio of 1:100 are prepared. The required amount of

Aerosil R972 is calculated by the formula of preparation (Table 2) and is placed in a pre-disinfected drum of the ball mill, then an alcoholic solution of benzalkonium chloride is added. The material is mixed at the velocity of

15 rpm for 30 min. The resulting powder is unloaded into metal boxes and dried at 60–70 °C until the alcohol is removed.

After drying, the bulk density of the material is controlled. To perform this, determine the weight and amount of semi-product in the cylinder filled to the “50” mark, after shrinkage for 10 min. The bulk density of the semi-product “Aerosil R972/benzalkonium chloride” should be between 230–240 g/L. The resulting semi-product is introduced into the sterile plastic container for bulk materials with accumulating it “in reserve”.

The IR spectrum of the semi-product “Aerosil R972/benzalkonium chloride” is shown at Fig. 2 b. In the spectrum of the intermediate there are absorption bands characteristic of both Aerosil R972 and benzalkonium chloride. We can distinguish bands of silanol groups  $3750\text{ cm}^{-1}$  (may indicate their incomplete replacement), a wide band OH oscillations of various forms of sorbed water (maximum about  $3400\text{ cm}^{-1}$ ) and deformation oscillations of water molecules ( $1640\text{ cm}^{-1}$ ), intense valence and weakly intense deformation vibrations of the groups  $-\text{CH}_3$  and  $-\text{CH}_2$ , which are present in benzalkonium chloride and on the surface of Aerosil R972.

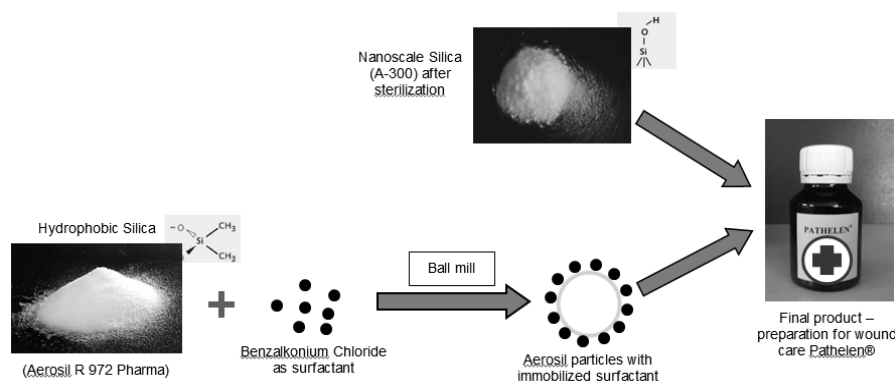
In the third stage the final product is obtained. Before the first loading of the mixer its space is disinfected. The amount of A-300 to be mixed with the intermediate obtained in stage 2 is calculated based on the load of 1/3 of the mixer volume. The calculated amount of A-300 prepared in stage 1 is placed in a mixer and stirred for 10 min. Then the required amount of semi-product obtained in stage 2 is added and stirred for 10–12 min. After that, not earlier than after 10 min the bulk density of the two samples

taken from the lower and upper layers of the composition, respectively, is determined. If a significant difference is found in the values obtained, stirring is continued until both values are in the range of 50–60 g/L. The final product (Pathelen®) is placed in sterile plastic container for bulk materials and the batch number is marked.

The IR spectrum of the final product is shown at Fig. 2 c. There are present all the major absorption bands as in the semi-product (Fig. 2 b), changing only their intensity. An increase in the intensity of the silanol groups Si–OH and a simultaneous decrease in the intensity of C–H oscillations is associated with an increase in the content of starting A-300 in the final product.

In this way, another problem was solved, which consisted in the non-uniformity of the composition at various points of its volume after mixing. This problem is aggravated by a significant difference in the bulk density of the components, A-300 (40–50 g/L) and the semi-product “Aerosil R972/benzalkonium chloride” (230–240 g/L). In industry, this problem is solved, for example, by granulation of one of the components. In our case, we used a simpler technological principle, namely, preliminary fluffing of A-300. To found the exact value of the bulk density, you must have a standard sample – a composition weighing 2.0 g, made from precise weighed portions of the components by intensive shaking in a 60 mL vial. The reference indexes for bulk density and sorption capacity for each individual batch of product depend on the indices of the initial A-300.

The entire drug manufacturing process is shown schematically in Fig. 3.



**Fig. 3.** The scheme of manufacturing process of hydrophilic/hydrophobic composition based on the nanoscale silica

**Quality Control.** Quality parameters are adapted to the requirements of Eur. Ph. Some parameters can be corrected later during re-tests of industrial batches of the product.

Accordingly to the visual examination, Pathelen® is a light, fine, amorphous powder, which transforms to a pseudo-liquid state after a sharp shaking of the vial half-filled with the drug (an air layer between the particles remains for some time, disrupting their adhesion). When shaken with water, it is not fully moistened.

Identification procedure of preparation includes three tests (A, B, C).

Test A is a reaction of silicates accordingly to the Eur. Ph. (2.3.1).

In the Test B, to 0.2 g of the preparation 5 mL of 1 M solution of sodium hydroxide is added and shaken until homogenous suspension is formed. The suspension is heated on a boiling water bath for 5 min and cooled. Then 0.1 mL of a 0.05 % solution of bromophenol blue and 5 mL of chloroform are added, shaken vigorously for 1 min and leaved for 15 min; the chloroform

layer turns blue (benzalkonium chloride). A blank experiment is carried out.

Accordingly to the Test C, the IR spectrum obtained in thin plates (size 28×5 mm, weighing 20–25 mg, prepared by pressing with a force of 2000 kg/cm<sup>2</sup>) in the range of 4000–400 cm<sup>-1</sup> shows a full correspondence to the IR spectrum of standard sample of preparation (Fig. 2 d).

Besides direct identification tests, some additional examinations are performed. Thus, bulk density which is determined as described in the technological part is normally 50–60 g/L and strongly depends on bulk density of initial A-300. The weight loss by calcination should not exceed 6.0 % for which 0.2000 g of the drug is heated in a platinum crucible at 900±50 °C for 2 h with a cooling in a desiccator before weighing. The loss of weight during calcination can be determined by thermal analysis as described in the technological part.

The microbial contamination of the preparation must comply the criteria given in the Table 3.

**Table 3.** Results of microbiology test of Pathelen® in comparison with the criteria adopted for products of this class

Microorganisms	Acceptance criteria for microbial quality accordingly to Eur. Ph. (5.1.4)	Results of test	
		Batch # 1	Batch # 2
Total aerobic microbial count (TAMC)	10 <sup>2</sup> CFU/g	55	15
Total combined yeast/mould count (TYMC)	10 <sup>1</sup> CFU/g	10	Less than 10
<i>Staphylococcus aureus</i>	Absent in 1 g	Absent in 1 g	Absent in 1 g
<i>Pseudomonas aeruginosa</i>	Absent in 1 g	Absent in 1 g	Absent in 1 g

CFU – colonia forming units

The adsorption capacity must be not less than 140 mg of protein per 1 g of the drug. To 0.6 g of gelatin (Eur. Ph.) in a volumetric flask with a volume of 100 mL add 60 mL of water, after 30 min heat at 60–70 °C, cool and dilute with water to 100.0 mL (standard solution containing 6.0 mg/mL of gelatin, is used freshly prepared). To 0.08 g of the drug in test-tube add 10.0 mL of standard solution of gelatin, close the stopper and shake for 1 h. Centrifuge for 20 min and filter. Then 4.0 mL of biuret reagent (Eur. Ph.) add in three test-tubes each containing 1.0 mL of water (blank experiment), 1.0 mL of the filtrate (examined solution) and 1.0 mL of

the standard solution (solution for comparison). The solutions are stirred after each addition and, after exactly 30 min, the absorbance at 540–560 nm is measured against the blank.

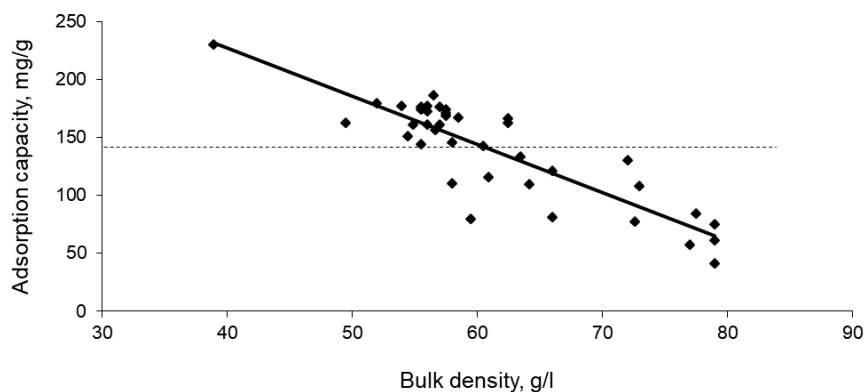
The amount of adsorbed gelatin in milligrams per 1 gram of the drug is calculated by the formula:

$$\frac{(A_0 - A) \cdot 60}{A_0 \cdot m},$$

where  $A_0$  – absorbance of the solution for comparison;  $A$  – absorbance of the examined solution;  $m$  – mass of the preparation to be examined in grams.

It has been found that there is a correlation close to linear between the adsorption capacity of the composition and its bulk density. Fig. 4 shows the results of measurements of these indices for various batches of the final product, including non-standard ones, obtained during the optimization of the manufacturing process. As can be seen, samples with low adsorption capacity have an overestimated bulk density, which, in turn, is a consequence of the increased

content of the dense semi-product “Aerosil R972/benzalkonium chloride” that does not adsorb proteins. Thus, bulk density control is considered as an express method to check the quality of a composition preparing. Of course, it is necessary to have a standard sample prepared using A-300 involved in the manufacture of this one batch of product (preparation of a standard sample is described in the technological part).



**Fig. 4.** Linear correlation ( $R = 0.87$ ) between adsorption capacity and bulk density for various samples of the final product. The leftmost point on a straight line belongs to the A-300

The presented quality control methods are intended for testing the drug in bulk. In case of its manufacturing as a finely packaged drug, additional requirements are set for containers and the uniformity of the content and mass of the drug in a container unit.

### CONCLUSIONS

In contrast to the topical application of antibiotic ointments, there is sorption treatment of infected wounds, especially in elderly patients with incurable ulcers on the background of diabetes. We have substantiated the method of wound cleaning with the auxiliary composition of two highly dispersed silicon-containing

sorbents, one of which has hydrophilic properties and the other – hydrophobic. Pathelen® preparation, which has been created specifically for EU consumers, includes hydrophilic A-300, hydrophobic Aerosil® R972 Pharma and the cationic surfactant benzalkonium chloride. The original technology of manufacturing an innovative drug based on the mechanochemical process and methods of quality control have been developed.

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## Гідрофільно-гідрофобний ранозагоювальний препарат на основі нанорозмірного кремнезему: фізико-хімічний та технологічний аспекти

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Лікування інфікованих виразок і ран, особливо у літніх людей, становить серйозну проблему у сучасній хірургії. В результаті багаторічних зусиль ми створили та починаємо клінічне вивчення інноваційної композиції для лікування ран, що має високі адсорбційні, протизапальні та ранозагоювальні властивості. Композиція, яка отримала назву *Pathelen®*, містить нанорозмірний гідрофільний кремнезем (A-300), гідрофобний кремнезем (*Aerosil® R972 Pharma*) та хлорид бензалконію. Метою роботи є опрацювання оптимальної технології промислового виробництва, а також методів контролю якості препарату.

Для вивчення напівпродуктів виробництва та кінцевого продукту було залучено вимірювання насипної густини, термічний аналіз, ІЧ-спектроскопію, хімічні методи ідентифікації, визначення адсорбційної активності та мікробіологічні дослідження.

Розроблено спосіб виробництва *Pathelen®*, який полягає у механохімічній іммобілізації хлориду бензалконію на поверхні гідрофобного кремнезему та змішування отриманого напівпродукту з гідрофільним нанорозмірним кремнеземом. Таким чином, запропоновано технологічний метод для поєднання гідрофільних та гідрофобних наноматеріалів в одному препараті. Кінцевий продукт відповідає встановленим показникам якості. Зокрема, насипна густина становить 50–60 г/л, адсорбційна активність – не менше 140 мг білка на грам препарату. Доведено відсутність патогенних мікроорганізмів та грибків, кількість непатогенних мікроорганізмів відповідає вимогам Європейської Фармакопеї для продуктів цієї категорії.

Отримані результати можуть бути корисними для організації у майбутньому широкомасштабного виробництва запропонованого препарату.

**Ключові слова:** лікування ран, адсорбція, нанорозмірний кремнезем, гідрофобний кремнезем, виробничий процес, контроль якості

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