# DEVELOPMENT OF THE POWDER COMPOSITION WITH THE SORBING, ANALGESIC AND ANTIMICROBIAL ACTIVITY BASED ON NATURAL ZEOLITE

**Rybachuk V. D., Ruban O. A.**

**National University of Pharmacy, Kharkiv**
**v.d.rybachuk@gmail.com**

**Introduction.** Active lifestyles, sports, participation in hiking trips and various competitions, as well as performing certain types of physical labor can cause traumatizing or injuring. Therefore, hyperactive children, and above all adolescents, professional athletes and representatives of certain occupations fall into the category of people in a high- risk group. Damage of the person's skin, regardless of the size and depth of the wound, requires immediate treatment with antiseptic or antimicrobial drugs, and it is very important for preventing infection of the wound surface. In addition, it is often necessary to reduce pain as the wo- und can deliver discomfort and interfere with the comfortable performance of any activity. For this purpose, pharmaceuticals are used in the form of lotions, gels, ointments, creams, aerosols and powders. Today the issue regarding the most convenient form of medicine that is applied to the wound remains controversial. Liquid do- sage forms provide a quick, but short-term effect, they are characterized by the lack of a high and prolonged osmotic activity, which sometimes limits their use, especially in the phase I of the wound process [1, 2]. Recently, soft dosage forms on the hydrophilic base remain the dominant group by frequency of application since fat bases prevent the flow of the exudate from the wound, contributing to the inflammatory process progression. Despite their numerous benefits the important drawback of using ointments is their painful application. Powders for the skin application are used for this purpose unreasonably rare [3].

Powders for skin application are a solid dosage form for external use consisting of a powder mix with a particle size less than 100 microns. Such powders are used for the treatment of acute inflammatory skin diseases, hygienic purposes on the skin with increased salivation, protection of the skin from external irritations, someti- mes for better fixation of ointments and pastes on the skin. Powders have several advantages over other forms of medicines. They are easily and painlessly applied to the wound and removed from it. When applied to the wound they provide a uniform distribution of active pharmaceutical ingredients on the surface of the wound, and it leads to a prolonged action [4].

There are special requirements to the powders applied on the wound surface. They should have sufficient adhesion, hold on the surface and prevent microbial invasion of wounds, have moderate adsorbing properties, reduce pain sensation, not undergo proteolytic cleavage and help the wound healing time reduction [3]. Currently, there are practically no medicines in the form of powders that would meet all these requirements [5]. Therefore, the issue of creation of new pharmaceuticals in the form of powder satisfying the specified requirements is relevant for modern medicine and pharmacy.

Nowadays, natural minerals, which have the most valuable properties due to the content of various macro- and microelements, are used in the powder compositions [6]. The natural zeolite is one of them. Natural zeolite (clinoptilolite) is a mineral of a group of water aluminosilicates having a framework structure, which main components are alkaline metal ions. It does not dissolve in water and biological fluids of an organism, and also has a high adsorption and the ion exchange ability, is capable of absorbing the exudate, pathogenic microorganisms and toxins, thereby cleansing the surface of the wound and facilitating its healing. It is also capable to withstand thermal sterilization. These qualities allow it to be used as an excipient (filler) when developing new formulations of sorption-active pharmaceutical forms [7-9].

**The aim** is to select the composition of active substances and excipients for creating a powder for the skin application with the sorbing, analgesic and antimicrobial activity based on natural zeolite.

## Materials & methods

The study objects were model powder compositions containing a filler (natural zeolite), local anesthetic (pyromecain), antifriction substances (talc, magnesium oxide, silicon dioxide) and antimicrobial substances (neomycin sulfate and polymyxin B sulfate). According to the literature antifriction substances were added in the amount of 1-10 % (0.25-2.5 g). Such insignificant content was chosen to provide only an improvement of the technological properties of the zeolite powder. The concentration of the antimicrobial components was chosen in the previous studies, but not in this work. The general composition of the samples is given in Tab. 1.

**Table 1. The general experimental composition of powders**

| Ingredients | The contents per one pack, 25.0 g |
|---|---|
| Natural zeolite (clinoptilolite), g | Up to 25.0 |
| Neomycin sulfate, IU/g | 5000 |
| Polymyxin B sulfate, IU/g | 10000 |
| Pyromecain, % (g) | 1-10% (0.25-2.5) |
| Antifriction substances, g | 1-10% (0.25-2.5) |

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To assess the technological properties of the experimental compositions the bulk density and the flowability were determined. The bulk density (g/cm3) (ρ0) and the tapped density (ρ1250) were calculated as the mass ratio to the corresponding powder volume using a Pharma Test PT-TD200 (Germany) device (the State Pharmacopoeia of Ukraine (SPhU), section 2.9.34 [10]). The flowability was determined by the method of a funnel with a vibration device using a device VP-12A (Ukraine), by the method of the SPhU, section 2.9.16 [10], as well as the Hausner ratio (H) and the Carr index (C) (SPhU, 2.9.36 [10]) using the following formulas:

$$H_R = \frac{\rho_{1250}}{\rho_0};$$

$$I_C = \frac{\rho_{1250} - \rho_0}{\rho_{1250}} \times 100.$$

The adsorption capacity of the powder to moisture was determined by dialysis through a semipermeable membrane. As a liquid medium 0.9% sodium chloride solution was used.

**Results & discussion**

The first stage of our research was the selection of the type and concentration of a local anesthetic. The most common domestic anesthetics used for this purpose are anesthezin, novocaine, dicain, lidocaine and pyromecain [11]. Analyzing literary data on the properties of these substances we rejected anesthesin due to its insolubility in water and slow beginning of anesthesia; dicain and novocaine due to their high toxicity, and the latter also due to the high risk of allergic reactions and low anesthetic properties; lidocaine due to its ability to inhibit the wound healing rate. Instead, our attention was attracted by pyromecain, an anesthetic of the amide group. It is 2,4,6-trimethylaniline-1-butyl-pyrrolidinecarboxylic acid-2 hydrochloride. Pyromecain is a white or whitebrownish colored powder that dissolves in water and alcohol. For pharmacological purposes, pyromecain is used for surface anesthesia; it is not inferior to lidocaine by the depth and duration of its action, while it is less toxic. Anesthesia with the use of pyromecain comes on the 2nd minute and reaches its maximum on the 10-15 minutes. The depth of anesthetic penetration is 3-4 mm. In addition, pyrimecane exhibits the analgesic and anti-inflammatory effects. The pyromecain concentration was chosen in vivo by the Rainier method. The essence of the method is in changing the sensitivity of the eye cornea to the action of mechanical irritation after introduction of the suspension of the powder behind the lower eyelid of the rabbit's right eye. The start time of the anesthetic and its duration was recorded. The experimental data obtained are shown in Fig.

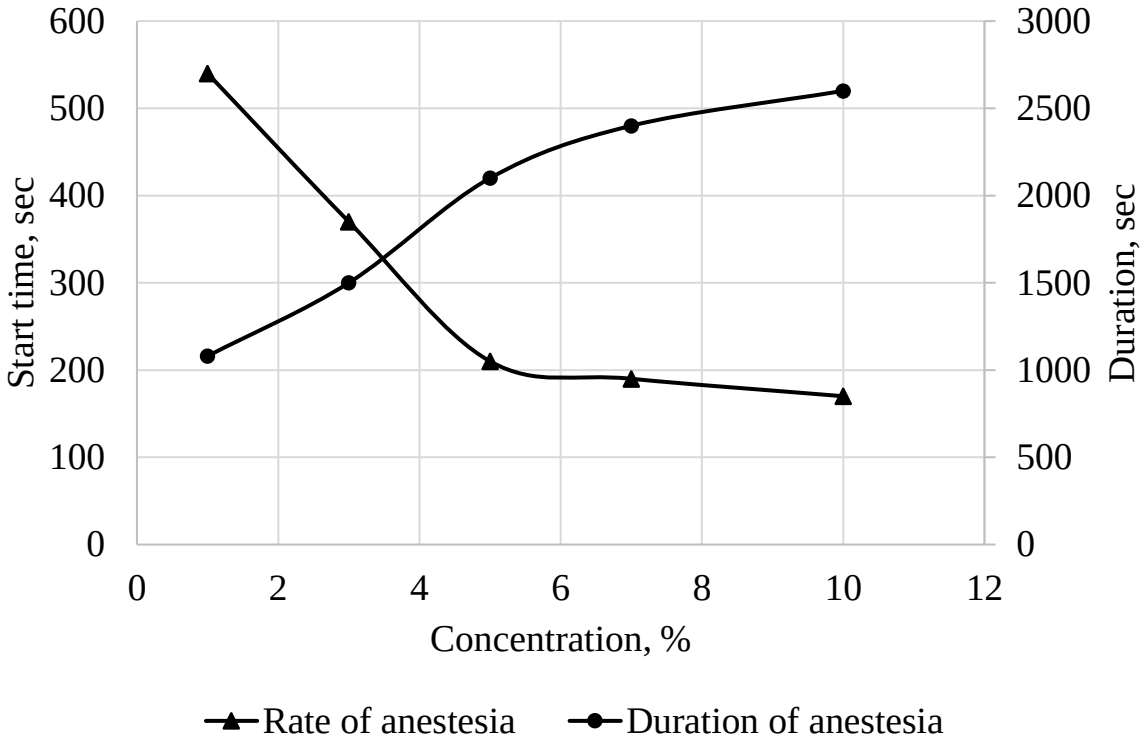


**Fig. The dependence of the start time and duration of anesthesia on the concentration of pyromecain**

As experimental data shows that the start time and duration of anesthesia depends on the content of anesthetic in the formulation. With an increase in the concentration from 1% to 10% the start time of the effect decreased from 540 seconds to 170 seconds, and the duration, on the contrary, increased from 1080 seconds up to 2700 seconds. The greatest reduction in the start time of anesthesia was when the concentration changed in the range of 1-5 %, and its further increase did not significantly increase the effect. It should also be mentioned that with increasing the concentration of pyromecain up to 5 % there was a noticeable increase in

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the duration of the effect, and the subsequent increase in the duration of anesthesia with an increase in the concentration was insignificant. Taking into account the foregoing the concentration of pyromecain in the composition of the powder developed was chosen for further research at the level of 5 %.

From our previous studies it is known that natural zeolite has a poor flowability. Therefore, taking into account the special use of a powder for the skin as a dosage form we considered that it was necessary to introduce antifriction substances into its composition. After the analysis of the literature data and formulations of industrially manufactured powders to improve the zeolite flowability we chose talc, magnesium oxide and silicon dioxide. The optimal excipient and its amount were chosen by the ability to improve the technological properties of the samples studied. The experimental data obtained are given in Tab. 2.

**Table 2.The effect of the concentration of antifriction substances on the technological properties of powders**

| Indicator | Concentration, % | | | | |
|---|---|---|---|---|---|
| | 1 | 3 | 5 | 7 | 10 |
| Talc | | | | | |
| Samle | № 1 | №2 | №3 | №4 | №5 |
| Bulk volume, $cm^3$ | 168,5 | 165,5 | 157,5 | 150,8 | 138,5 |
| Tapped volume, $cm^3$ | 110,8 | 110,3 | 107,8 | 106,9 | 101,8 |
| Bulk density, $g/cm^3$ | 0,59 | 0,60 | 0,63 | 0,66 | 0,72 |
| Tapped density, $g/cm^3$ | 0,90 | 0,90 | 0,92 | 0,93 | 0,98 |
| Flowability, 100 g/sec | 69,4 | 64,5 | 57,6 | 52,6 | 48,4 |
| $H_R$ | 1,52 | 1,50 | 1,46 | 1,41 | 1,37 |
| $I_C$ | 34,2 | 33,3 | 31 | 29,1 | 26,5 |
| Magnesium oxide | | | | | |
| Samle | № 6 | №7 | №8 | №9 | №10 |
| Bulk volume, $cm^3$ | 157,8 | 147,5 | 133 | 130,2 | 126,7 |
| Tapped volume, $cm^3$ | 101,2 | 98,5 | 95,75 | 94,5 | 92,5 |
| Bulk density, $g/cm^3$ | 0,63 | 0,72 | 0,75 | 0,77 | 0,79 |
| Tapped density, $g/cm^3$ | 0,99 | 1,02 | 1,04 | 1,06 | 1,08 |
| Flowability, 100 g/sec | 72,2 | 70,5 | 68,7 | 66,2 | 65,7 |
| $H_R$ | 1,55 | 1,4 | 1,39 | 1,38 | 1,36 |
| $I_C$ | 35,8 | 28,36 | 28 | 27,4 | 27,3 |
| Silicon dioxide | | | | | |
| Samle | № 11 | №12 | №13 | №14 | №15 |
| Bulk volume, $cm^3$ | 163,6 | 181,8 | 210 | 227,5 | 234,5 |
| Tapped volume, $cm^3$ | 102,2 | 135,5 | 161 | 182 | 198 |
| Bulk density, $g/cm^3$ | 0,61 | 0,55 | 0,48 | 0,44 | 0,42 |
| Tapped density, $g/cm^3$ | 0,98 | 0,74 | 0,62 | 0,55 | 0,51 |
| Flowability, 100 g/sec | 40,6 | 33,5 | 26,7 | 21,7 | 19,8 |
| $H_R$ | 1,59 | 1,34 | 1,3 | 1,25 | 1,18 |
| $I_C$ | 37,5 | 26,4 | 23,3 | 20 | 15,5 |

The analysis of the data obtained showed that adding talc and magnesium oxide to the powder mixture resulted in a decrease in the bulk and tapped volume by 18-19 % and 8-9 %, respectively, compared to the natural zeolite powder [8]. Moreover, these indicators decreased with an increase in the concentration of excipients in the mixture. Conversely, the value of the bulk and tapped density for mixtures with talc and magnesium oxide increased by 2-18 % and 2-3 %, respectively, due to the higher density compared to zeolite. Addition of silicon dioxide, unlike other excipients used, led to an increase in the values of bulk volumes and, consequently, to a decrease in densities. The bulk and tapped volume increased by 30 % and 48 %, respectively, while the bulk and tapped density decreased by 31 % and 47 %, respectively, with an increase in the concentration of silicon dioxide from 1 % to 10 %. It can be explained by the low values of the density of this excipient.

The study of the effect of various concentrations of talc, magnesium oxide and silicon dioxide on the flow-ability of the experimental samples of the powder showed that this parameter was influenced by all the excipients. The most significant improvement occurred when adding silicon dioxide. In general, in order of decreasing the effect these substances can be placed in the following sequence: silicon dioxide > magnesium oxide > talc. An increase in the values of flowability when adding the excipients used was within the whole range of concentrations. The greatest changes in flowability occur- red when the concentration of silicon dioxide increased in the range of 1-5 %. Estimation of flowability by values of the flow chart relative to HR and IC [12] showed that samples with talc and magnesium oxide belonged to categories of substances with a poor and unsatisfactory fluidity. Sample 11 with silicon dioxide is characterized by a poor flowability, samples 12 and 13 have satisfactory fluidity, and sample 14 is also

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satisfactory, while sample 15 has a good flowability. It should be also noted that when preparing model samples of powders with silicon dioxide we observed a significant layering of mixtures containing more than 5 % of silicon dioxide. Therefore, despite the better fluidity of samples 14 and 15 we selected sample 13 with 5 % silicon dioxide content for further research. The use of powder requires its retention on the surface of the skin after application, therefore, the permissible fluidity and high adhesion of the sample in this case is not a disadvantage.

The final stage of our research was the study of the adsorption properties of the composition developed. The experimental data obtained are shown in Tab. 3.

**Table 3. Adsorption properties of the composition developed**

| Sample | The amount of the liquid absorbed, % |
|---|---|
| Natural zeolite powder | 61 |
| Powder developed (sample №13) | 73 |

The data obtained indicate that the adsorption capacity of the powder developed in relation to the solution of sodium chloride exceeds the similar properties of natural zeolite apparently due to the presence of silicon dioxide, and is generally characterized as moderate. The moderate osmotic properties of the powder will allow using it at the stage of the wound process, which is characterized by insignificant discharge of the exudate, and at the stage of the wound granulation.

Thus, as a result of our complex studies the following composition was proposed: natural zeolite (clinoptilolite) – up to 25.0 g, neomycin sulfate – 5000 IU/g, polymyxin B sulfate – 10,000 IU/g, pyromecain – 1.25 g (5 %) and silicon dioxide – 1.25 g (5 %).

CONCLUSIONS

1. The analysis of the scientific literature has found the importance of developing a domestic pharmaceutical preparation in the form of a powder based on natural zeolite for application on the skin.

2. As a result of the complex experimental studies the medicated product in the form of a powder for external use has been developed. The product proposed contains a natural mineral (natural zeolite), antimicrobial (neomycin sulfate and polymyxin B sulphate) and anesthetic substances (pyromecain) and silicon dioxide, and possesses a moderately sorbing, antimicrobial and analgesic action. It can be used for the treatment and prevention of skin diseases accompanied with infection and exudation.

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**Introduction.** An active lifestyle, playing sports, participating in hiking trips and various competitions, as well as performing certain types of physical labor may be accompanied by injury. Damage of the skin requires its immediate treatment. Powders are an alternative to soft dosage forms, which are usually used for this purpose. Powders are used in acute inflammatory skin diseases, with a hygienic purpose in increased sweating and sebum secretion, to protect the skin from external irritations, as well as for better fixation of ointments and pastes on the skin. **Aim.** To select the composition of active substances and excipients for creating a powder with the sorbing, analgesic and antimicrobial activity

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based on natural zeolite. **Materials & methods.** The study objects were model powder compositions containing a filler (natural zeolite), anesthetic (pyromecain), antifriction substances (talc, magnesium oxide, silicon dioxide) and antimicrobial substances (neomycin sulfate and polymyxin B sulfate). The quality of the samples was assessed by indicators of bulk and tapped densities, flowability, the Hausner ratio (H) and the Carr index (C). The osmotic activity was assessed by dialysis through a semipermeable membrane. For performing the tests the methods of the State Pharmacopoeia of Ukraine (SPhU) were used. **Results & discussion.** Powders with 5 % pyromecain showed the most optimal properties by the time of the start and duration of anesthesia; however, a further increase in its concentration did not give a significant effect. The technological properties of powders depend on both the type and concentration of antifriction substances. The addition of talc and magnesium oxide increased the density of powders by 2-18 %, and silicon dioxide reduced the density by 31-47 %. The flowability (100 g/s) of samples with talc was 48.4-69.4, with magnesium oxide – 65.7-72.2, and with silicon dioxide – 19.8-40.6. The most significant improvement in flowability occurred after adding silicon dioxide; therefore, this substance in the amount of 5 % was chosen for further research. The adsorption properties of the powder were characterized as moderate. The osmotic activity was 73 %. **Conclusions.** The studies on selection of active substances and excipients for creating a powder with the sorbing, analgesic and antimicrobial action based on natural zeolite have been conducted. The following composition of the medicinal product has been proposed: natural zeolite (clinoptilolite) – up to 25.0 g, neomycin sulfate – 5000 IU/g, polymyxin B sulfate – 10.000 IU/g, pyromecain – 1.25 g (5 %) and silicon dioxide – 1.25 g (5 %).

**Keywords:** natural zeolite; powder; excipients; pyromecain; osmotic activity

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