Научно-практический журнал
ФАРМАЦИЯ И ФАРМАКОЛОГИЯ

ОРИГИНАЛЬНАЯ СТАТЬЯ

DOI: 10.19163/2307-9266-2019-7-5-279-290

MORPHOLOGICAL, TECHNOLOGICAL AND BIOPHARMACEUTICAL STUDIES OF ALGINATE-CHITOSAN MICROCAPSULES WITH VINPOCETINE

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Received 25 September 2019 Review (1) 10 October 2019 Review (2) 15 October 2019 Accepted: 21 October 2019

The aim of the investigation is to study morphological, technological and biopharmaceutical properties of alginate-chitosan microcapsules with Vinpocetine.

Materials and Methods: Alginate-chitosan microcapsules with different concentrations of sodium alginate (0.5%, 1%, 1.5%, 2%, 2.5% and 3%) and a medium viscosity chitosan solution (0.25–0,5%), as well as microcapsules not treated with a solution of chitosan, were obtained. The surface morphology was studied by methods of atomic-powered microscopy with the use of an NT-MDT Corporation probe scanning microscope (model Solver P47 Pro). To study biopharmaceutical properties of the obtained microcapsules, the "Rotating Basket" apparatus was used.

Results: It has been found out that the microcapsules not treated with a chitosan solution, have a smooth, transversely striated surface with large heights and deep cavities. With an increase in the concentration of sodium alginate, the surface becomes smoother, the peaks become larger, higher and wider, the cavities get deeper and more sinuous. The microcapsules treated with a chitosan solution, on the contrary, have a rough surface, low heights and shallow cavities, and with an increase in the concentration of sodium alginate, the surface becomes rougher, the heights are evenly distributed along the microcapsule. The spectrophotometry method was used to determine the efficiency of microencapsulation and the release rate of Vinpocetine from the microcapsules per unit time. When the concentration of a sodium alginate solution is 2.5%, the efficiency of microencapsulation is maximum (86.8%). At this concentration, saturation occurs and with its further increase, the efficiency decreases. The maximum release rate of Vinpocetine from microcapsule samples is observed when the concentration of a sodium alginate solution is 1%: it amounts to 41.17%.

Conclusion. The amplitude parameters of the microcapsules surface are different at different concentrations. There is a pattern of alternating signs of asymmetry and excess in the samples with chitosan. With a change in the scale of scanning, the surface characteristics of the microcapsules change. The most distinctive details of the structure are visible at the scale of 2 × 2 μm^2. At the concentration of sodium alginate of 2.5%, the efficiency of microencapsulation is maximum (86.8%). Studying the effect of the concentration of a sodium alginate solution on the release rate of Vinpocetine from the microcapsule samples has shown that at the concentration of 1%, the release rate is 41.17%, and at the concentration of 2.5% it is 4.5%. These microcapsules can be used in order to produce capsules with modified release.

Keywords: sodium alginate, chitosan, alginate-chitosan microcapsules, atomic-powered microscopy, amplitude parameters, microencapsulation efficiency, release rate

For citation: Morphological, technological and biopharmaceutical studies of alginate-chitosan microcapsules with vinpocetine. Yu.A. Polkovnikova, N.A. Severinova, K.N. Koryanova, U.A. Tulskaya, M.V. Grechkina. *Pharmacy & Pharmacology*. 2019;7(5): 279-290. **DOI:** 10.19163/2307-9266-2019-7-5-279-290

Для цитирования: Ю.А. Полковникова, Н.А. Северинова, К.Н. Корянова, У.А. Тульская, М.В. Гречкина. Морфологические, технологические и биофармацевтические исследования альгинат-хитозановых микрокапсул с винпоцетином. *Фармация и фармакология.* 2019;7(5): 279-290. **DOI:** 10.19163/2307-9266-2019-7-5-279-290

RESEARCH ARTICLE

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

МОРФОЛОГИЧЕСКИЕ, ТЕХНОЛОГИЧЕСКИЕ И БИОФАРМАЦЕВТИЧЕСКИЕ ИССЛЕДОВАНИЯ АЛЬГИНАТ-ХИТОЗАНОВЫХ МИКРОКАПСУЛ С ВИНПОЦЕТИНОМ

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Получено 25.09.2019 Рецензия (1) 10.10.2019 Рецензия (2) 15.10.2019 Принята к печати 21.10.2019

Цель: изучение морфологических, технологических и биофармацевтических свойств альгинат-хитозановых микрокапсул с винпоцетином.

Материалы и методы. Получены альгинат-хитозановые микрокапсулы с различной концентрацией натрия альгината (0,5%, 1%, 1,5%, 2%, 2,5% и 3%) и раствором хитозана средней вязкости (0,25–0,5%), а также микрокапсулы, не обработанные раствором хитозана. Исследования морфологии поверхности проводились методом атомно-силовой микроскопии с помощью сканирующего зондового микроскопа корпорации NT-MDT модели Solver P47 Pro. Для изучения биофармацевтических свойств микрокапсул использовался аппарат «Вращающаяся корзинка».

Результаты. Установлено, что микрокапсулы, не обработанные раствором хитозана, имеют гладкую, поперечно исчерченную поверхность с крупными высотами и глубокими впадинами. С увеличением концентрации натрия альгината поверхность становится более гладкой, пики – крупнее, выше и шире, впадины – глубже и более извилистыми. Микрокапсулы, обработанные раствором хитозана, напротив, имеют шероховатую поверхность, небольшие высоты и неглубокие впадины, и с увеличением концентрации натрия альгината поверхность становится более шероховатой, высоты равномерно распределяются в микрокапсуле. Методом спектрофотометрии определена эффективность микрокапсулирования и степень высвобождения винпоцетина из микрокапсул в единицу времени. При концентрации раствора натрия альгината 2,5% эффективность микрокапсулирования максимальна (86,8%). При данной концентрации происходит насыщение и при её дальнейшем увеличении эффективность снижается. Максимальная степень высвобождения винпоцетина наблюдается из образцов микрокапсул с концентрацией раствора натрия альгината 1% и составляет 41,17%.

Заключение. Амплитудные параметры поверхности микрокапсул имеют отличия при разных концентрациях. Существует закономерность чередования знака асимметрии и эксцесса у образцов с хитозаном. При изменении масштабов сканирования происходит изменение характеристик поверхности микрокапсул. Наиболее чётко отличительные детали структуры видны при масштабе 2×2 мкм^2. При концентрации натрия альгината 2,5% эффективность микрокапсулирования максимальна (86,8%). При изучении влиянии концентрации раствора натрия альгината на степень высвобождения винпоцетина из образцов микрокапсул установлено, что при концентрации 1% степень высвобождения составляет 41,17%, а при 2,5–4,5%. Данные микрокапсулы можно использовать для изготовления капсул с модифицированных высвобождением.

Ключевые слова: альгинат натрия, хитозан, альгинат-хитозановые микрокапсулы, атомно-силовая микроскопия, амплитудные параметры, эффективность микрокапсулирования, степень высвобождения

INTRODUCTION

In recent years, more and more significance has been attached to the complexes with chitin and chitosan throughout the world. Studies of their quantitative and qualitative analyses have been conducted, as well as the production of these polymers, their physicochemical properties and the possibility of expanding the use of chitin and chitosan in medicine [1]. One of the most promising and actively developing areas in pharmacy and pharmacology is the development of controlled delivery of drugs [2, 3].

Studies on the formation of a film coating based on chitosan with the inclusion of antibiotics, are also being conducted [4].

In addition to the studies of drug complexes with chitosan, the use of chitosan itself as a medicine is of scientific interest. In the course of studying the effect of chitosan on a model of contact allergic dermatitis, it has been found out that by using photophoresis, chitosan is able to reduce the concentration of metal in the skin of the experimental animals. These results indicate the effectiveness of chitosan in the treatment of skin diseases [5–8].

Chitosan is a natural polycationic, linear polysaccharide, a derivative of chitin. It is a universal biomaterial due to the lack of toxicity and good biodegradability and biocompatibility. Mixtures of high purity chitosan mono-, poly- and oligomers act as regenerative, wound healing

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2019-7-5-279-290

and antitumor drugs. Chitosan exhibits a wide range of positive properties, which makes it possible to use it in various fields of biomedical science [9–13].

The use of chitosan as a nanocarrier of drugs is a promising area of science, since chitosan-drug complexes are more resistant to destruction under the influence of the internal environment of the body, and also increase the delivery of the drug to the target unchanged.

A water-soluble and biodegradable polymer, sodium alginate is often used as a coat [14]. As a polymer for microcapsules, sodium alginate is widely used. In one of the studies, sodium alginate was used in the form of a 2% solution to obtain microcapsules with a bacteriophage. An innovative enteric-soluble dosage form that can be used as an antibacterial drug, has been obtained [15–17].

Atomic-powered microscopy (APM) is one of the most advanced methods for studying surface properties. Traditionally, this method is used to determine the surface morphology of various objects with high spatial resolution. The study of the roughness of microcapsules is carried out to prove that the true surface area is most often more geometric, since it is affected by the structure of the microrelief. Processing the data on the surface relief makes it possible to deeply analyze its various characteristics [18–20].

THE AIM of the investigation is to conduct morphological, technological, and biopharmaceutical studies of alginate-chitosan microcapsules with Vinpocetine.

MATERIALS AND METHODS

Alginate-chitosan microcapsules with various concentrations of sodium alginate (0.5%, 1%, 1.5%, 2%, 2.5% and 3%) and a medium viscosity chitosan solution (0.25–0.5%), as well as microcapsules not treated with a solution of chitosan, have been studied. Obtaining the samples of microcapsules was carried out by extrusion.

The surface morphology was studied by methods of atomic-powered microscopy with the use of an NT-MDT Corporation probe scanning microscope (model Solver P47 Pro) (Zelenograd, Russia).

Scanning was performed by HA_NC cantilevers (for microcapsules without chitosan with 0.5% and 1% concentrations of sodium alginate), by HA_FM (for microcapsules without chitosan with 2% and 3% concentrations of sodium alginate) and by NSG03 (for microcapsules without chitosan with 1.5% and 2.5% concentrations of sodium alginate for microcapsules with chitosan with all used concentrations of sodium alginate).

The length was 90 ± 5 μm, the resonant frequency was (260 ÷ 630) kHz and the radius of the curvature of the probe tip was 10 nm. The experiments were carried out in air at the temperature of 25 ± 1°C. The scanning fields reached (5 × 5) μm^2 with the difference in the elevation of the relief of no more than 2.5 μm. Using a probe and an atomic-powered microscope scanner, it was possible to obtain surface images with the lateral resolution up to 10 nm and the vertical one up to 1 nm.

Visualization of the measurement results consisted in representing the relief in the form of three-dimensional images. Processing of the obtained APM images was carried out with the use of ACM Solver P47 Pro Nova RC1 software and consisted in the analysis of the amplitude average statistical parameters of the surface roughness in accordance with international standards:

1) R_a – arithmetic average roughness;
2) R_q – quadratic mean roughness;
3) R_z – maximum profile height;
4) R_{sk} – asymmetry;
5) R_{ku} – excess.

To determine the true and geometric surface areas of the microcapsules, processing of the obtained APM images was performed using Gwyddion 2.11 software.

The efficiency of microencapsulation was determined by the “direct” method. For the direct determination, the actual content of Vinpocetine in microcapsules after microencapsulation was calculated. For this, a sample of microcapsules was dissolved in 0.0 1 M HCl, heated for 20 minutes, then cooled down, and the volume was adjusted to the mark with the same acid.

Using the spectrophotometry method, the optical density of the resulting solution was determined at the absorption maximum of 312 nm.

After determining the amount of Vinpocetine released during the dissolution, knowing its initial concentration, the microencapsulation efficiency was calculated taking into account the amount of $m_{caps.}$ included in the microcapsules, the initial amount of the substance that was dissolved – $m_{init.}$ according to the formula:

$$E = m_{caps.} / m_{init.} * 100\% \quad (1)$$

The study of biopharmaceutical properties was carried out in accordance with General Pharmacopoeial Monograph 1.4.2.0014.15. Using the spectrophotometry method, the optical density of the obtained solutions was determined with an absorption maximum of 314 ± 2 nm at each sampling stage.

RESULTS AND DISCUSSION

Microcapsules are medium-weight large opaque isodiametric (equiaxed) yellowish-white or yellow crystals. They have good flowability, which is the basic feature for the process of capsules manufacturing.

A comparison of the microcapsules surface and their microprofiles with different concentrations of sodium alginate, treated with a solution of chitosan and without this treatment, is shown in Figs. 1–6.

In Fig. 1a, the surface has a characteristic longitudinal striation, protrusions and cavities of various heights and depths, respectively. The structure is homogeneous, there are no visible inclusions, the outer surface is smooth. In Fig. 1b the surface is cellular, wrinkled, rough. There are small protrusions**.** On the microprofile with chitosan (Fig. 1c), a pronounced surface relief with a

wavy surface is visible, the peaks are smoothed. There is no microprofile without chitosan, since the surface does not have any characteristic relief features.

In Fig. 2a, the surface is slightly rough, it has a rare longitudinal striation, deep cavities and gently-sloping wrinkled heights. In Fig. 2b microcapsules have a transversely wrinkled structure. The surface is smooth, there are deep cavities, pits and voluminous pointed protrusions. The surface micro profiles are similar. Both are sharply scattered at maxima and minima of heights. The peaks are slightly serrated. There are practically no visible differences in the relief structure.

In Fig. 3a, the surface is very rough, with protrusions of different heights and widths. The cavities and pits are small. At the top of the heights there are rare small spherical inclusions. On the ups and downs, the surface is longitudinally wrinkled. In Fig. 3b, the surface is smooth, sporadically it has a longitudinal striation. There are single rocky and spherical inclusions of different sizes, as well as groups of such inclusions. The cavities are practically absent, but there are small protrusions and ups. The microprofile of the surface with chitosan (Fig. 3c) has a less smoothed surface, but smaller elevation differences, as well as serrated peak tops, than the microprofile without chitosan (Fig. 3d).

In Fig. 4a, the surface is slightly rough, there are characteristic high peaks found in the groups with a wide base and a pointed apex. The pits are shallow, but long. In Fig. 4b, the surface is uneven, rough, with numerous spherical protrusions and inclusions. The microprofile of microcapsules with chitosan (Fig. 4c) has an abrupt relief, which differs significantly from the microprofile without chitosan (Fig. 4d) characterized by a sawtooth surface.

At the given concentration of sodium alginate, the differences in the surface of microcapsules with and without chitosan begin to come out.

In Fig. 5a, the surface is wrinkled, slightly cellular, and there are no visible inclusions. In Fig. 5b, the surface of the microcapsule is smooth, with long, winding, shallow pits. The protrusions are large, gentle, with a slight transverse striation. There are no inclusions. Microprofiles (Figs. 5c and 5d) have characteristic differences. The surface with chitosan has a coarse-toothed profile with narrow and finely serrated peaks, and without chitosan, on the contrary, it is more even and smoother, and has also a wavy smooth appearance. The amplitude profile parameters for the samples (see Table 1), vary greatly with respect to each other, which makes it possible to consider the differences between microcapsules with and without chitosan.

In Fig. 6a, the microcapsule is highly wrinkled, covered with numerous pits. The surface is unevenly rough. There are gently-sloping heights of various shapes.

In Fig. 6b, the surface of the microcapsule is smooth, deeply sinuous, the protrusions are big, gently-sloping, transversely striated. There are no inclusions in them. In Fig. 6c, the microprofile has a coarse toothed appearance with elongated serrated peaks. The microprofile without chitosan is wavy, smoothed.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2019-7-5-279-290

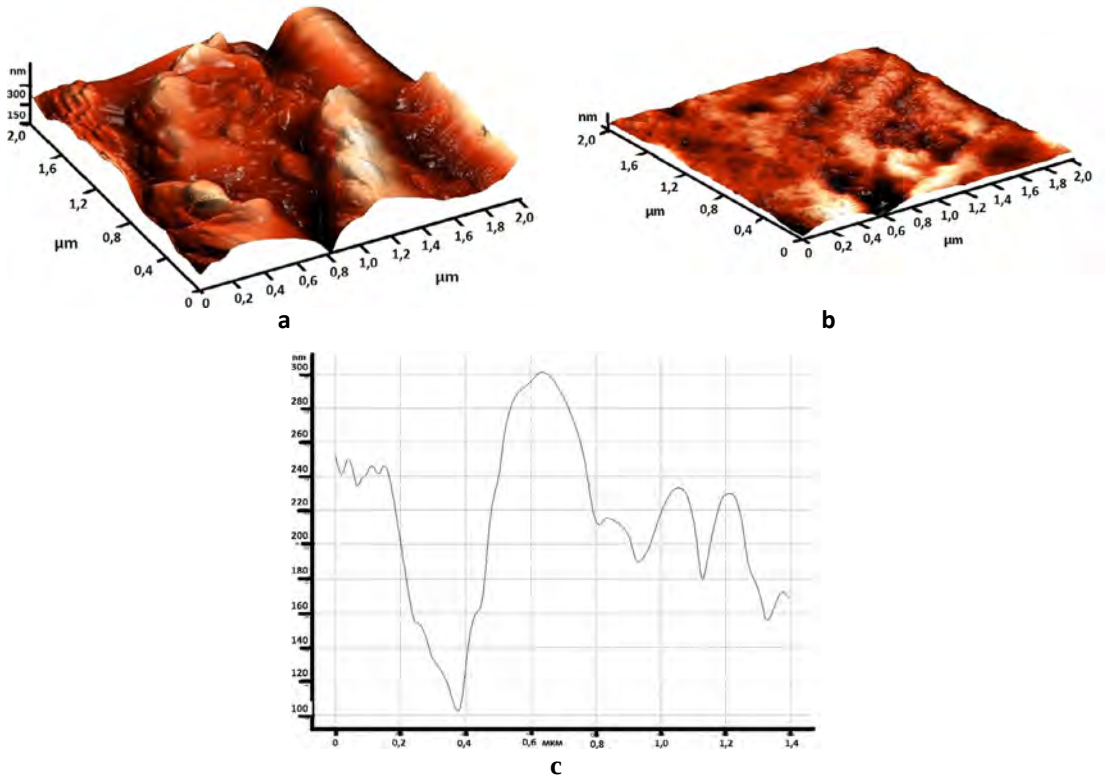
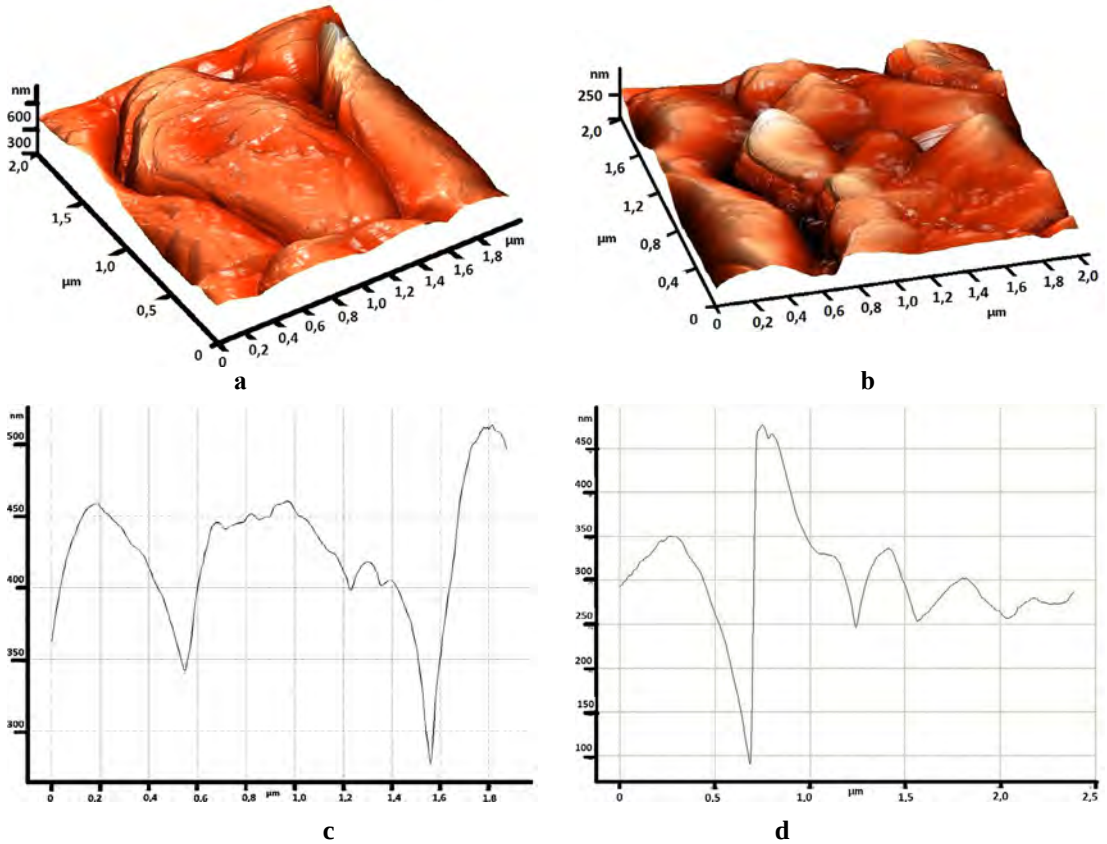


Figure 1 – Three-dimensional APM image of the microcapsules surface with a 0.5% concentration of sodium alginate treated with a chitosan solution (a), and its microprofile (c), and without chitosan (b), with a scanning area of 2 × 2 μm²



PFigure 2 – Three-dimensional APM image of the microcapsules surface with a 1% concentration of sodium alginate treated with a chitosan solution (a), and without chitosan, (b), and their microprofiles (c and d), with a scanning area of 2 × 2 μm²

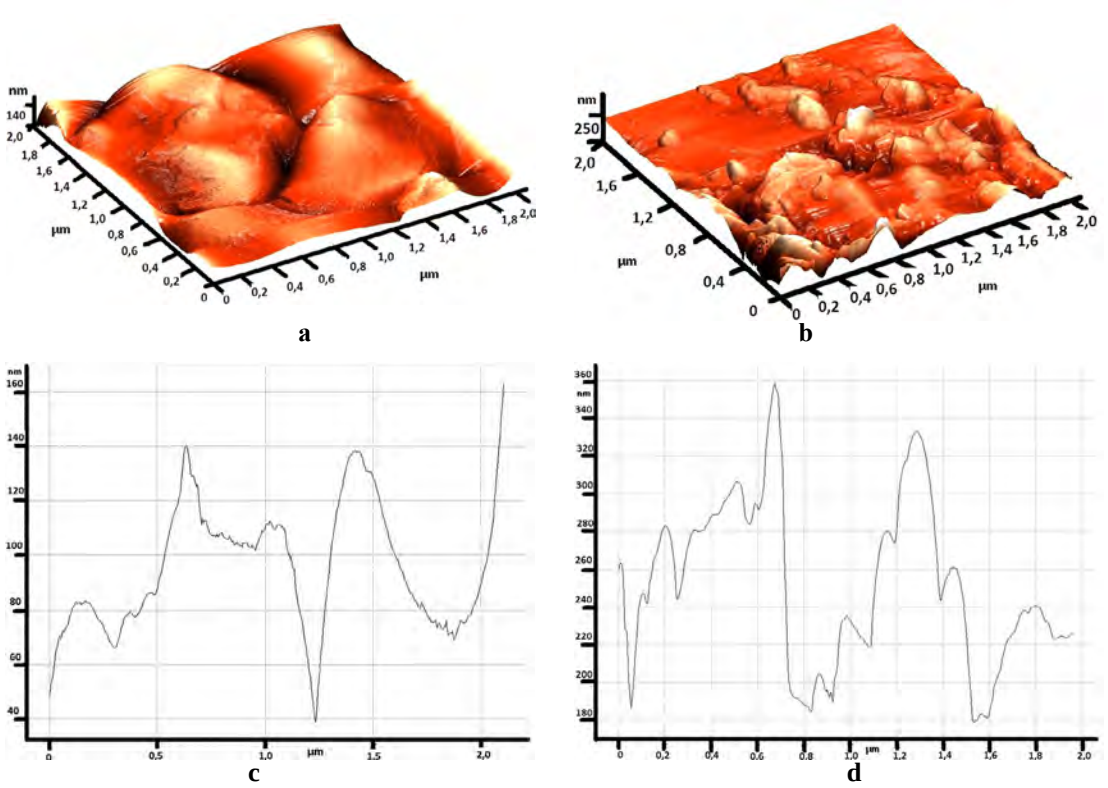


Figure 3 – Three-dimensional APM image of the microcapsules surface with a 1.5% concentration of sodium alginate treated with a chitosan solution (a), and without chitosan, (b), and their microprofiles (c and d) with a scanning area of 2 × 2 μm²

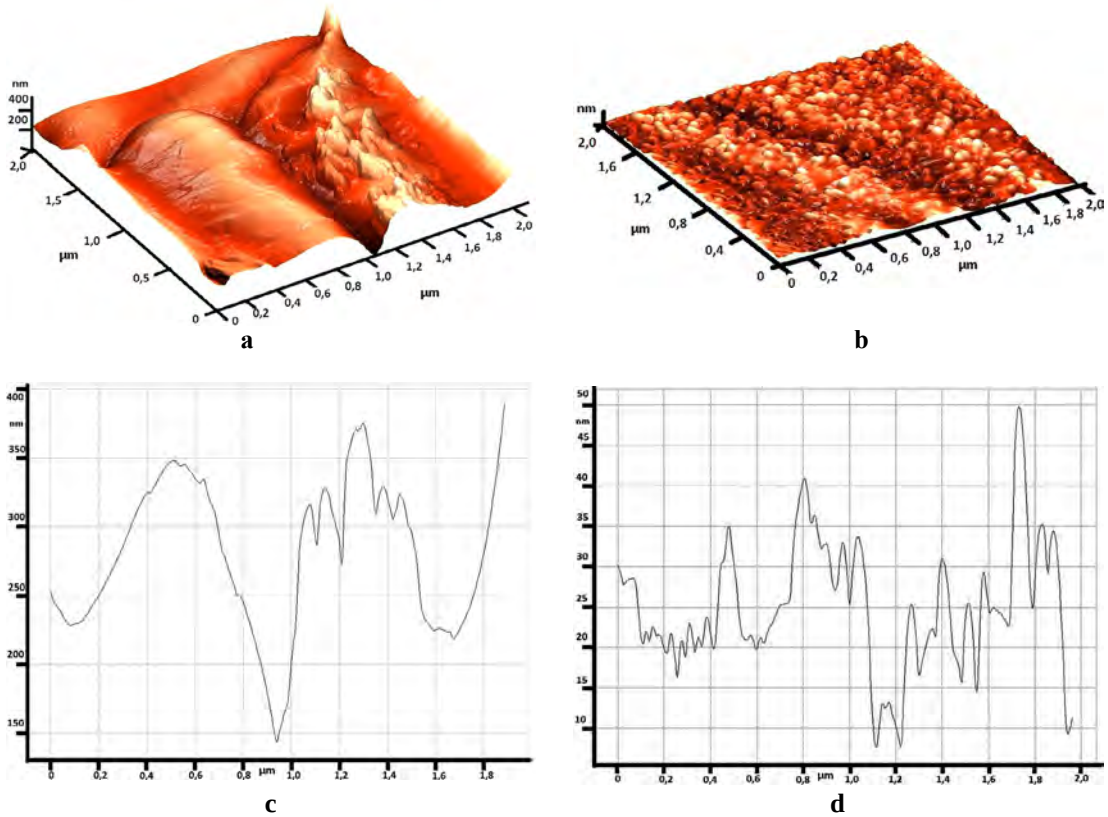


Figure 4 – Three-dimensional AFM image of the microcapsules surface with a 2% concentration of sodium alginate, treated with a chitosan solution (a), and without chitosan (b), and their microprofiles (c and d) with a scanning area of 2 × 2 μm²

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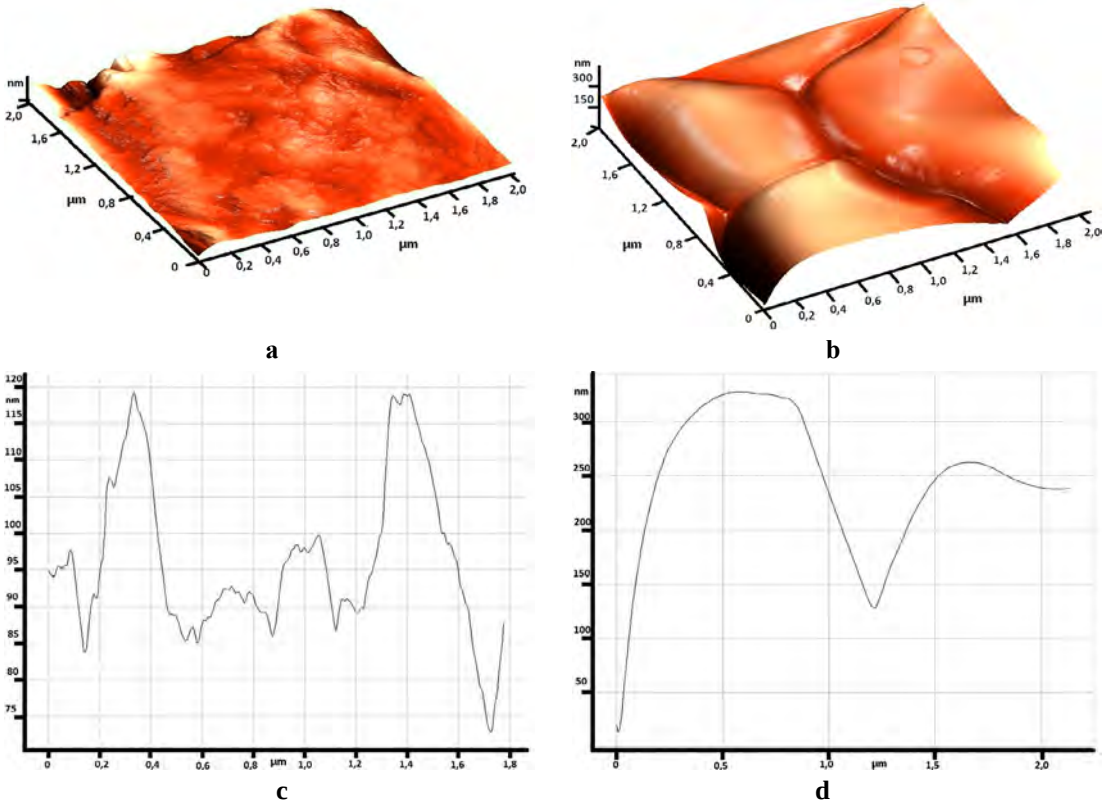

Figure 5 – Three-dimensional APM image of the microcapsules surface with a 2.5% concentration of sodium alginate treated with a chitosan solution (a) and without chitosan (b), and their microprofiles (c and d) with a scanning area of 2 × 2 μm²

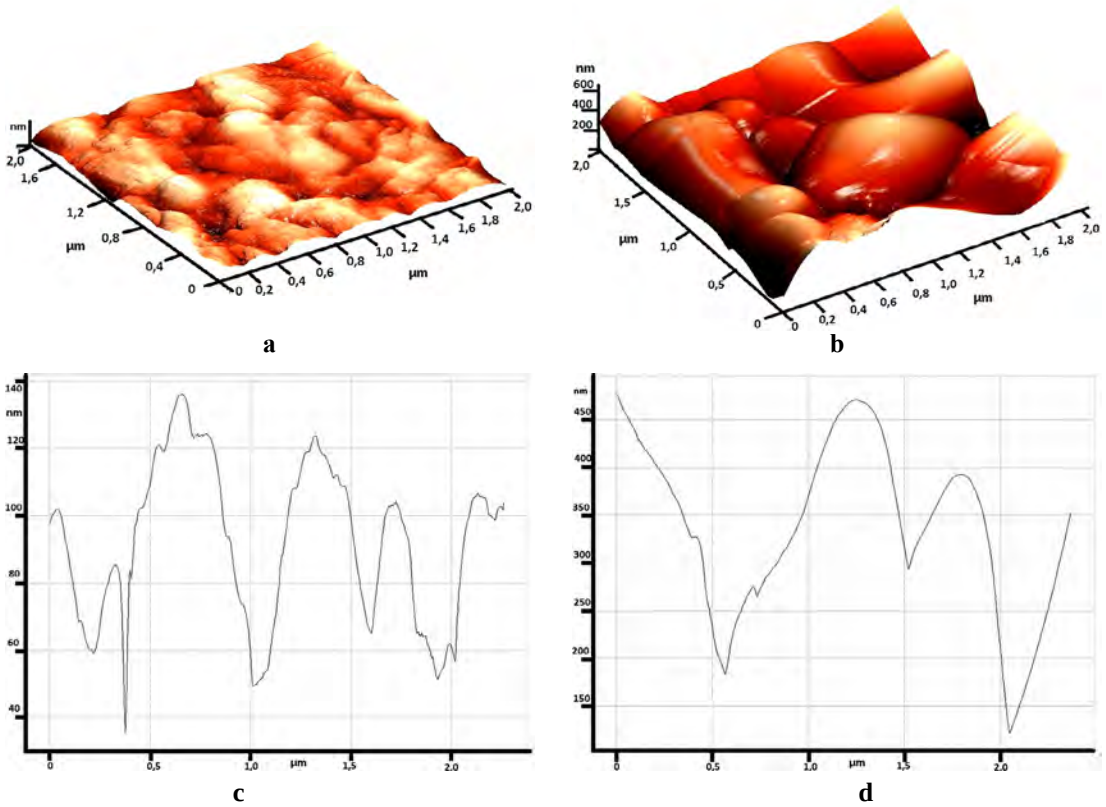

Figure 6 – Three-dimensional APM image of the microcapsules surface with a 3% concentration of sodium alginate, treated with a chitosan solution (a), and without chitosan (b), and their microprofiles (c and d) with a scanning area of 2 × 2 μm²

ISSN 2307-9266 e-ISSN 2413-2241
Scientific and Practical Journal
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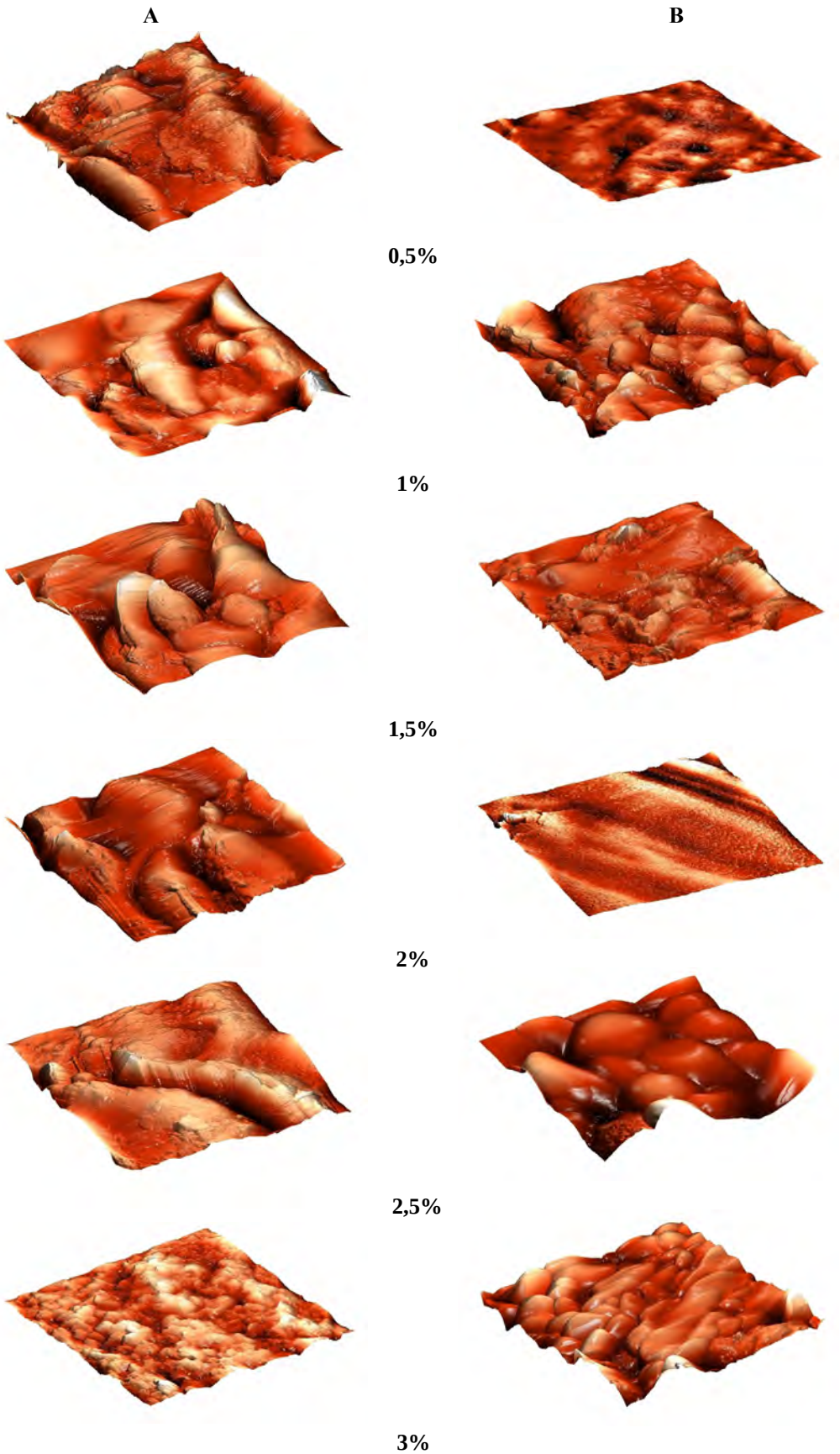

Figure 7 – Three-dimensional APM image of the microcapsules surface with different concentrations of sodium alginate treated with a chitosan solution (A) and without chitosan (B), with a scanning area of 5 × 5 μm²

ОРИГИНАЛЬНАЯ СТАТЬЯ
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Table 1 – Parameters of the surface roughness of the microprofile with a scanning area of 2 × 2 μm²

Concentration of sodium alginate solution	Type of microcapsules	R_z, nm	R_a, nm	R_q, nm	R_{sk}, nm	R_{ku}, nm
0.5%	With chitosan	199	41,8	51.4	−0.3	−0.5
	Without chitosan	–	–	–	–	–
1%	With chitosan	240	31.9	46.7	−1.5	3.6
	Without chitosan	390	49.2	73.5	0.1	2.6
1.5%	With chitosan	126	19.4	23.9	0.3	1.2
	Without chitosan	180	39.4	48.4	0.6	−0.4
2%	With chitosan	232	47.0	56.0	−0.4	−0.3
	Without chitosan	42	6.3	8.2	0.5	0.6
2.5%	With chitosan	46.5	8.3	10.8	0.8	0.1
	Without chitosan	314	57.4	85.9	−1.5	2.4
3%	With chitosan	101	24.8	27.2	−0.2	−1.4
	Without chitosan	680	77.8	95.8	−0.2	−0.6

The amplitude roughness parameters based on the microprofiles, were calculated. The results are shown in Table 1.

On the basis of the carried out studies it was found out that microcapsules not treated with a chitosan solution have a smooth, transversely striated surface with large heights and deep cavities. With an increase of the sodium alginate concentration, the surface becomes smoother, the peaks become larger, higher and wider, the cavities get deeper and more sinuous. The microcapsules treated with a chitosan solution, on the contrary, have a rough surface, small heights and shallow pits, and with an increase in the concentration of sodium alginate, the surface becomes rougher, the heights are evenly distributed along the microcapsule. At the sodium alginate concentrations of 0.5%, 1%, and 1.5%, the differences between microcapsules with and without chitosan are implicit, but at the concentrations of 2.0%, 2.5% and 3%, the characteristic features become clear. The microprofiles made it possible to calculate the necessary roughness parameters. The calculated data confirmed the differences in the surface character of the microcapsules. The samples with chitosan and 0.5%, 1%, 2% and 3% concentrations of sodium alginate, are characterized by negative asymmetry, which indicates that the distribution has a long left “tail” and a negative excess (except the 1% sample). Microcapsules without chitosan with a 1–2% concentration of sodium alginate have a positive asymmetry with close indicators, i.e. a long right “tail”. The samples with chitosan and without chitosan at the 1.5% concentration have different positive asymmetries at different excesses, and at the 3% concentration they have the same negative asymmetry with different but negative excesses. Some alternation of the asymmetry sign and excess is observed in the samples with increasing concentrations.

Below, Fig. 7 shows the surface of microcapsules with different concentrations of sodium alginate treated with and without a chitosan solution with a scanning area of 5 × 5 μm².

With a scanning area of 5 × 5 μm², one can also observe the manifestation of differences in the surface structure of microcapsules with and without chitosan, but clearly visible differences are noticeable only at 2.5% and 3% sodium alginate concentrations. At the concentration of 2%, vague characteristics are observed.

Besides, as far as the given scanning area is concerned, the characteristic and structural features of the microcapsules surface described above at different concentrations of sodium alginate, are less noticeable. As a result of that, it is difficult to distinguish microcapsules with and without chitosan at the concentration of 2%.

At the next stage of the research, the efficiency of microencapsulation was determined by spectrophotometry. Based on the data obtained, a graph of the dependence of the Vinpocetine microencapsulation efficiency on the concentration of sodium alginate has been constructed (Fig. 8).

So, at the 2.5% concentration of sodium alginate, the efficiency of microencapsulation is maximum – 86.8%. At this concentration, saturation occurs and with its further increase, the efficiency decreases.

As a result of the biopharmaceutical studies, carried out in the process of the microcapsules preparation, the effect of the concentration of a sodium alginate solution on the Vinpocetine release has been shown (Fig. 9).

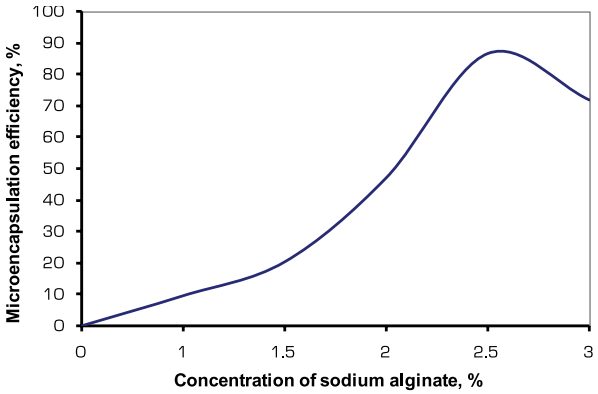

Figure 8 – Dependence of microencapsulation efficiency on the concentration of sodium alginate

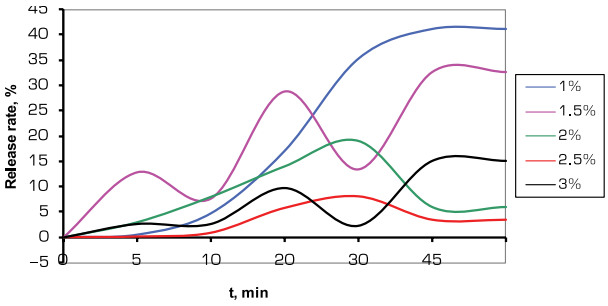

Figure 9 – Release rate of Vinpocetine from microcapsules

Table 2 – Technological properties of microcapsules

Test indicator	Methods of determination	Experimental values	Reference values
Microcapsules size	General Pharmacopoeial monograph 1.1.0015.15	1.0–2.0 mm 0.5–1.0 mm 0.2–0.5 mm (Medium, large and very large)	Very large: >1.4 mm Large: 0.355–1.4 mm Moderately fine: 0,18–0,355 mm Medium: 0.125–0.18 mm Very small: 0.09–0.125 mm
Microcapsules shape	General Pharmacopoeial monograph 1.2.1.0009.15	Equlaxial	Elongate: >3:1 Tabulate: 3:1 Equiaxed: 1:1
Flowability	General Pharmacopoeial monograph 1.4.2.0016.15	Loose weight density: 714.3 kg/m^3 (Medium)	Rather heavy: >2000 kg/m^3 Heavy: 1100–2000 kg/m^3 Medium: 600–1100 kg/m^3 Light: < 600 kg/m^3
		Flowability: 14.17 g/sec. (Good)	Excellent: 8.6–12.0 g/sec. Good: 6.6–8.5 g/sec. Satisfactory: 3.0–6.5 g/sec. Acceptable: 2.0–3.0 g/sec. Bad: 1.0–2.0 g/sec. Very bad: <1.0 g/sec.
		Angle of natural slope: 34° (Good)	Very good: 25–30° Good: 31–35° Satisfactory: 36–45° Poor: 46–55° Bad: 56–65° Very bad: >66°

The release rate of Vinpocetine from microcapsule samples with a 1% concentration of a sodium alginate solution is maximum and amounts to 41.17%. A slower release is observed from the microcapsules with a 2.5% concentration of a sodium alginate solution: by 45 minutes of the experiment it has been 4.5%.

Next, the technological properties of microcapsules were studied (Table 2).

The data obtained indicate that microcapsules are opaque, medium-weight large opaque isodiametric (equiaxed) yellowish-white or yellow particles with good flowability, which makes it possible to be used as fillers for encapsulated forms.

Thus, as a result of the carried out studies, model samples of Vinpocetine microcapsules were obtained. The method of atomic-powered microscopy was used to study morphological features of alginate-chitosan microcapsules. In the surface structure, the microcapsules treated with chitosan, have characteristic differences from the microcapsules without chitosan. The differences are most pronounced at the 2.5% and 3% concentrations of sodium alginate. Amplitude parameters are different at different concentrations. Negative asymmetry prevails in the sam-

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2019-7-5-279-290

ples with chitosan (0.5%, 1%, 2%, 3%), the excess is evenly distributed. The samples without chitosan are dominated by positive asymmetry (1%, 1.5%, 2%) and positive excess. There is a certain pattern of alternating the sign of asymmetry and excess in the samples with chitosan.

With a change in the scale of the scan, the surface characteristics of the microcapsules change, too. The most distinctive details of the structure are visible at the scale of 2 × 2 μm^2.

When the concentration of asodium alginate solution is 2.5%, the efficiency of microencapsulation is maximum (86.8%).

While studying the effect of the concentration of a sodium alginate solution on the release rate of Vinpocetine from the microcapsule samples, it was found out that at the concentration of 1%, the release rate is 41.17%, and at the concentration of 2.5% it is 4.5%. These microcapsules can be used to make modified release capsules.

CONCLUSION

Thus, it has been established that with an increase in the degree of microcapsules roughness, an increase in the efficiency of microencapsulation occurs. With an increase in the concentration of a sodium alginate solution, the release rate of the substance decreases. This can be explained by the fact that Vinpocetine has an affinity for sodium alginate, which binds it to the complex, and with an increasing concentration of a sodium alginate solution in an aqueous medium, the binding strength increases.

The results obtained during the study are promising for a further detailed study of microencapsulated vinpocetine in order to create its dosage forms.

FINANCIAL SUPPORT

The reported study was funded by RFBR according to the research project №19-315-50008

AUTHOR CONTRIBUTIONS

All authors have equally contributed to the research work.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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