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Properties and structure of gelatin composite films with amoxicillin microparticles

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Abstract. The degree of release of amoxicillin (AM) microparticles from composite gelatin-amoxicillin films at pH range 1–11 was investigated. Composite gelatin-amoxicillin films were fabricated by both Langmuir–Blodgett and spin-coating techniques. Microparticles prepared by spray drying method. It was established that the release degree of amoxicillin is maximum at pH=7.

1. Introduction
Modern developments in pharmacology are directed not only at creating new medicinal substances, but also at improving the properties of existing ones. The main objectives of developments are improvement of bioavailability and drug selective effect, reduction of side effects and usability. One of them is an obtainment of drug microparticles, which can be used in the production of inhaled and nasal forms of drugs, more particularly, forms of oral administration [1]. Microparticles with active substances incorporated into the polymer matrix (films, spheres, capsules) raise a great attention of chemical and pharmaceutical industries as prolonged action substances. Such microparticles of slow release of an active substance allow reducing the frequency of usage, while the concentration of an active substance remains constant for a long time. Films-carriers of an active substance can be used for dosed drugs delivery through a mucous membrane or skin into the systemic circulation. Often this method is used for the treatment of burns. The advantages of usage this type drugs are the reduction of side effects, rapid drug effect, the constant concentration of an active substance, the possibility to immediately stop treatment [2, 3]. The release of amoxicillin (AM) from both thin films and gelatin microparticles was investigated. Gelatin is a biocompatible polymer and can be used as a matrix-carrier of drugs in forms, such as composite microparticles and bandages doped active substances. The value of pH system vary depending on an application area, consequently, the release degree is also depends on the application specificity. The polymer matrix can be obtained from biocompatible and non-toxic components: high-molecular compounds of animal and vegetable origin, lipids, cellulose derivatives, synthetic polymers and oligomers, natural resins, polyester resins, etc [4]. The spray drying method is one of the most promising for production of composite microparticles. The essence of this method consists in obtaining particles from solutions or suspensions. Wherein liquid is sprayed into a hot medium, droplets are dried and quickly become solid (particles). The advantages of this

method are short drying time, one-step process, without requiring additional purification and processing of microparticles obtained [5].

2. Materials and methods

Amoxicillin (AM, Farmland, Republic of Belarus) and composite microparticles with gelatin were obtained by spray drying method. Spray dryer LU-222 Advanced device (LU-222 Advanced, Labultima, India) was used to obtain particles at parameters of the spray drying process: vacuum – 2100 Pa, drying air temperature – 170 ° C, nozzle fluid pressure – 4 kg/cm^2 [6].

For the investigation of the release processes the films of gelatin and gelatin/AM were obtained by Langmuir–Blodgett (LB) at surface pressures of 13 and 4 mN/m, respectively; and spin-coating methods with rotation speed of 8000 rpm during 2 minutes.

The structure of obtained films on silicon sustrates was investigated by atomic force microscopy (NT-206, Ltd “Microtest machines”, Republic of Belarus) and standard silicon cantilevers of NSC 11A with a hardness of 3 N/m.

The release of pure AM microparticles and composite microparticles including gelatin was evaluated by optical spectrophotometer in both hydrochloric acid and sodium hydroxide solutions in changing of pH value from 1 to 11 with step of 2. Wavelength – absorption spectra were recorded in the wavelength range from 200 to 800 nm using a Cary UV WIN 60 spectrophotometer (Agilent, USA). Cuvettes with the pathway of 10 mm were used during the experiment.

The peak of gelatin absorption appears at wavelengths of 230 and 270 nm. Insignificant shifts are possible depending on protein composition of the product. Absorbance spectrum of amoxicillin trihydrate is shown at wavelength of 254 nm. According to the literature [7], AM molecule contains phenolic hydroxyl, consequently, its absorbance spectrum depends on the media pH. The bathochromic shift of spectrum occurs in an alkaline media, with accompanying of a hyperchromic effect. The absorbance peak for the two types of compounds is identically, the spectra of the original AM and gelatin were recorded were taken for identifying substances. Then the release degree and disrupture of gelatin films were analyzed relative to control, based on obtained spectra of films and microparticles AM-gelatin under investigation.

3. Results and discussion

For gelatin at the pH range 1–11, it was established that there are peak wavelength in the wavelength range from 210 to 270 nm, at that the peak wavelength is indicative under such conditions as pH 7, the wavelength of 440 nm that occurs during the dissociation of –COOH and the formation of -COO- groups and also the appearance of a negative charge. The dependence of the solubility of gelatin from the media pH has a saddle-like character (the solubility is minimal nearby at isoelectric point), that appears due to polymorphic properties, such as the minimum swelling occurs at pH value of 4.7 (nearby at isoelectric point), at a time when the maximum swelling – at pH value of 3.2. In an acidic media, such as at pH<4.8, the dissociation of –COOH groups is inhibited and -NH_2 groups are protoned to become $NH3^+$. Gelatin molecules acquire a positive charge. The charge change of macromolecules leads to the change of their conformations and it is required that an acid superfluity (pH< 7) to accomplish the isoelectric point in the gelatin solution and to inhibit of –COOH groups ionization.

For the initial AM, peaks were identified at wavelengths from 230 to 280 nm at pH 1 and 3 – from 205 to 280 nm, which proves the existence of it in the trihydrate form. It was established that there are additional peaks for composite AM microparticles with gelatin at pH 1 and pH 3 at wavelengths of 325 and 390 nm, respectively. Believes that an additional interaction of gelatin proteins with AM molecules is taken place during the spray drying process, at that the dissociation of amoxicillin molecules arises in the acidic media. During the investigation of composite AM micriparticles with sodium chloride at all pH range, the peak is appeared at wavelength of 325 nm. At the same time, smaller size AM microparticles with gelatin in the size range of 1–3 μm can be characterized by a most peaks numbers in comparison with particles of 3–5 μm in size, which related to the gelatin dissolving process. The concentration of AM microparticles is max at pH 7, and the release of gelatin proteins in the resulting solution is taken place at pH 1 and 3, that appears in the presence of peaks in absorbance spectra, indicating to gelatin.

The AM release from gelatin composite thin films formed by LB and spin-coating techniques has the similar character, a max quantity at pH 7, then the decrease of release degree at pH 5 and 9, and further increasing at pH 1 and 11. The rate of swelling and dissolving is higher for more thin films fabricated by LB technique than spin-coating films.

The obtained results are consistent with AFM research. As a result of keeping the samples in acidic media, the morphology of the gelatin films changed. A large number of conglomerates are formed with a diameter from 0.5 to 1 μm. It was established that the areas of different diameter clusters are formed due destruction of the film (figure 1).

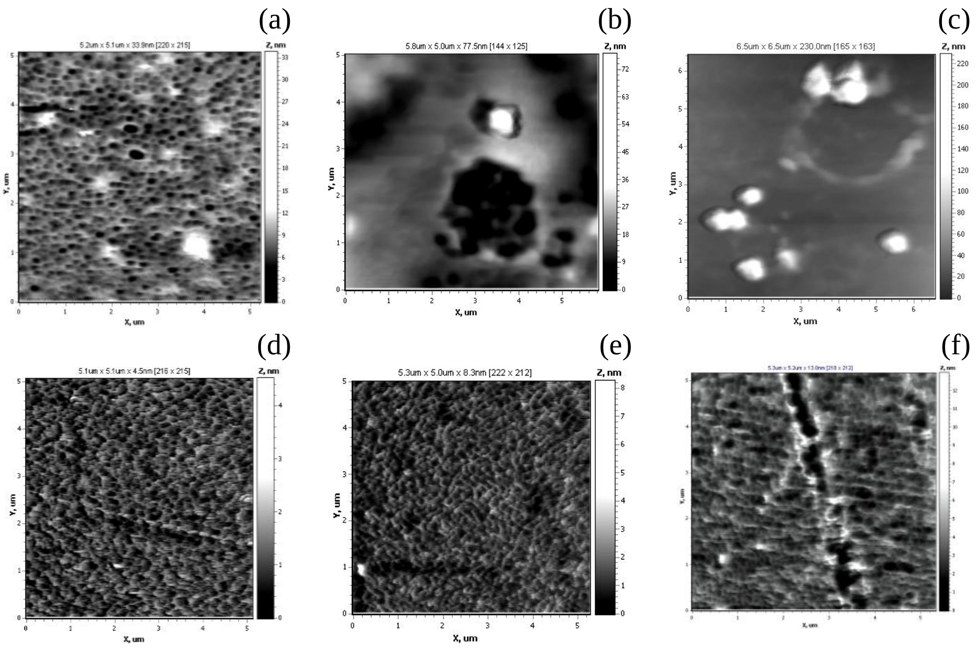

Figure 1. Structure of LB-films of gelatin (a)–(c), gelatin with AM (d)–(f) at pH 1 (b), (e) and pH 3 (c), (f).

According to the films structure investigated after the keeping in media from pH 1 to 11, processes of a disrupture passes max in the acidic media. There is the functional groups answer, situated on the investigated film surface for films formed by LB procedure. The most probable that the film formation occurs with the orientation of carboxylic group to inside of a surface, because LB films was fabricated onto silicon substrates by means of preliminary hydrofilization of it in the ammonia-peroxide solution. The amino group of gelatin proteins remains vacant and, as was described above, undergoes to the disrupture, increaseng of the dissolving degree film in solutions.

A maximum number of peaks appear at pH 1 and 3. Doping of AM intensify the peak at high-frequency wavelength. LB films of gelatin, including AM, form a denser layer onto silicon substrates in comparison with pure gelatin films. The disrupture of composite AM films with gelatin is observed by AFM only at pH 3 in the form of structural packings, and also particles formation with size approximately 400 nm.

The local formation of gelatin conglomerates is noted after the films ageing at pH range 5−11, as that the presence of crater areas is not reducing; gelatin film remains stable to the disrupture. Samples of gelatin films, obtained by spin-coating method, form a dense layer onto the surface of silicon substrates with a mean square roughness of 0.5 nm. The films are obtaining by this method differs from those formed by the LB method (figure 2).

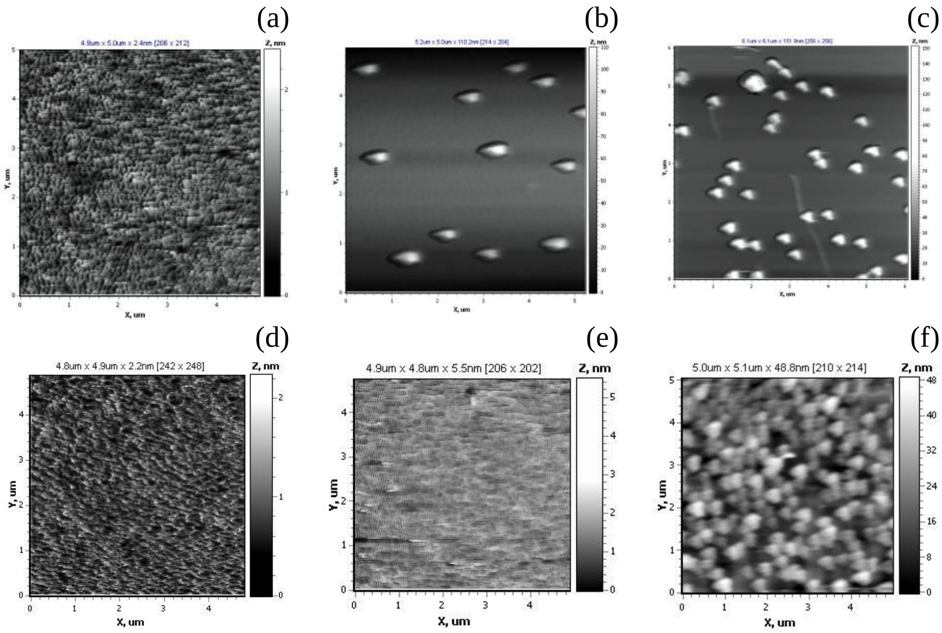

Figure 2. The structure gelatin films of (a)–(c), gelatin with AM (d)–(f), obtained by spin-coating, at pH 1 (b), (e) and pH 3 (c), (f).

The characteristic craters haven't been established, and the keeping in acidic solutions at pH 1 leads to gelatin dissolution with conglomerates formation in size of 200–300 µm. With increasing solution acidity, the gelatin films dissolution rises as well as a number of conglomerates grows. Composite films gelatin with AM are less susceptible to degradation at pH 1, the release degree is less than 3 times in comparison with LB films.

4. Conclusion

As a result of the research, it was established that LB gelatin films with AM form denser structure in comparison with pure gelatin films and more stable. The release degree of AM is maximum at pH 7. The obtained films can be used for dose delivery of different type's antibiotics through the mucous membrane or the skin into the systemic circulation.

The obtained results can be used for the investigation of the biocompatibility and kinetics of the dissolution of different type's drugs in medicine, with development of drugs delivery systems.

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References

[1] Mukhina M A and Leonova M V 2012 *Medical business* 1 **23** 16–22
[2] Osikov M V, Simonyan E V, Grigorieva G P, Saedgalin O T and Nozhkina N N 2014 *Fundamental research* 1632
[3] Romanova O L 2010 *Zemsky doctor* **2** 25
[4] Postrish J V and Khishova O M 2010 *Messenger of Pharmacy* 2 **48** 73
[5] Kedik S A and Sapelnikov M D 2014 *Messenger of Voronezh State University. Series: Chemistry. Biology. Pharmacy* **2** 28–32
[6] Radyukevich D L, Melnikova G B and Chizhik S A 2018 *Collection of abstracts of the V Republican initial technical conference of young scientists Gomel, Polikomtrib* 28
[7] Zhernosek A K, Zhebentyaev A I and Talut I E 2014 *Analytical chemistry. Chemical methods of analysis: study tutorial* 542