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THE STUDY OF ADSORPTION AND DESORPTION OF ANTIBIOTICS ON THE SURFACE OF NANOPARTICLES

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Abstract: Nanotechnology is a field that is gaining more and more importance in the modern world. It is noted that the use of nanoparticles (balls with a diameter of from several to several hundred nm) as carriers of drugs gives an opportunity for their controlled and sustained release (1, 2). Nanoparticles as a potential drug carrier for sustained release may enhance the effectiveness of antibiotics. In order to examine the effects of antibiotics with nanoparticles, an attempt was made to deposit on them three drugs differing in chemical structure. These were chloramphenicol, gentamicin and ceftazidime. The aim of this study was to determine the degree of adsorption of the drug on the surface of nanoparticles and to examine the process of desorption from the surface of silica nanoparticles. The results of the study indicate that in the case of chloramphenicol it is essentially a process of chemisorption, and for gentamicin and ceftazidime both physical and chemical adsorption, without there being any clearly defined relationship between this two processes. The purpose of the nanoparticles as drug carriers is to obtain controlled and prolonged exposure to the drug. Ceftazidime, as the compound with the largest number of double bonds and a large number of groups that can form hydrogen bonds (carbonyl, amino groups), was the most adsorbed.

Keywords: silica, nanoparticles, adsorption, antibiotics, drug, carrier

The basic method of preparation of silica nanoparticles is the sol-gel method. It involves the use of two chemical processes: hydrolysis of tetraethoxysilane (TEOS), other alkoxysilanes or polycondensation (1, 2).

The reactions are carried out in ethanol medium at pH 11-12, obtained by addition of ammonia (ammonia is also a catalyst influencing the process of hydrolysis and polymerization) (3, 4, 5). The optimal conditions for the silica nanoparticles synthesis are shown in Table 1.

With the presence of hydroxyl groups on the surface, nanoparticles are not recognized by opsonins as elements foreign to the body. These proteins are not joined to the surface, so these nanoparticles are not captured by the reticuloendothelial system (RES), in contrast to polymeric nanoparticles, which to avoid capture by the RES must have a modified surface. Frequently this involves connecting to the surface of polyoxyethylene or polyethylene glycol groups. Biocompatibility of silica nanoparticles allows them to feed the body, without the prior modification of their surface (7, 8).

Silica, creating nanoparticles, is resistant to the action of enzymes in the blood and other tissues of the body, which are responsible for the degradation of polymeric nanoparticles. Thus, they are no longer maintained in the body and at the same time no longer release the drug substance. Furthermore, nanoparticles are stable in a wide pH range and resistant to temperature changes. This stability, however, can be a problem due to the accumulation of nanoparticles in certain organs, causing damage (8).

Silica nanoparticles have a very large surface area, often reaching several hundred m^2/g. This is due to the presence of numerous pores. This is what makes nanoparticles able to adsorb on its surface a relatively large amount of various substances such as drugs, hence their use as a catalyst for the drug substance with a controlled and delayed release. The nanoparticles' surface properties largely determine the process for their preparation, since conditions depend primarily on the particle diameter and the number, diameter and depth of the pores. For adsorption of drugs to be effective, nanoparticles

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should have a highly functional external and internal surface (7-9).

The relationship between release rate and the presence of suitable functional groups on the surface may allow the design of nanoparticles with which the drug will be released in the best, most therapeutically favorable kinetics (10). A major problem today is to maintain pharmacotherapy drug concentration at the right level at the right place, exactly where the disease process is pending. Nanoparticles have a chance to solve it. It has already been shown that providing sustained release nanoparticles and nanosphere type used to have a significant effect on the rate of releasing process of the active substance (9). Nanoparticles as drug carriers can increase their durability. This is due to the fact that the drug is "trapped" in the pores of the carrier, where dispersive factors (such as oxygen, oxidizers, aqueous solutions of acids or bases) have extremely difficult access (11). Research is conducted mainly on anticancer drugs, which, through the nanoparticles, can be precisely placed on the tumor, and, gradually releasing it, maintain its concentration at the appropriate level. The big disadvantage of some anticancer drugs such as camptothecin and paclitaxel is their very low solubility in water. The solution to this problem may be silica nanoparticles that are used as carriers, resulting in therapeutic concentrations of the drug at the target site without the need for organic solvents (10-13).

The amount of adsorbed substance is affected by the pore size of the adsorbent. The smaller pore size, the more effective is the adsorption, but only until the average pore diameter is large enough to be able to penetrate the adsorbate particles. There are two basic types of physical and chemical adsorption (14).

Both processes can occur in parallel. This is where both the solvent and the substance dissolved therein are adsorbed on the adsorbent surface to form various bonds. The desorption phenomenon can be defined as the inverse process of adsorption. Desorption can occur only in the case of physical adsorption when the interaction between adsorbent and adsorbate are not too strong (14).

Table 1. Optimal conditions for the synthesis of nanoparticles of size 30 nm [6].

Parameter	Value
H_2O/TEOS	30-55
NH_3 [mol/L]	0.2-0.35
The rate of addition of TEOS [cm^3/min]	13-17
Temperature [^oC]	55-65

Table 2. The results of the adsorption medium to the surface of chloramphenicol silica nanoparticles. (The results in the tables have been rounded to the fourth decimal place).

Initial concentration of the solution [mg/mL]	0.0325	0.0245	0.0216	0.0190	0.0154	0.0063
Average amount of drug adsorbed from 6 measurements [mg]	0.0036	0.0034	0.0047	0.0069	0.0032	0.0013
% Average of 6 measurements adsorbed	10.9744	13.9456	21.6821	36.4035	20.5628	14.1577

Table 3. Statistical analysis of the correlation values used to plot the Langmuir adsorption isotherm (L) and Freundlich (F) for chloramphenicol. (The results in the tables have been rounded to the fourth decimal place).

		Average	Std. stand.	r	r^2	t-test	p	N
L	C_A [mg/mL]	0.0166	0.0076					
	$C_{0\text{-}C\,A}$ [mg]	4.2047	4.7536	0.8320	0.6923	2.9997	0.0340	6
F	Log C_A	-1.8218	0.2031					
	Log ($C_{0\text{-}C\,A}$)	-2.4687	0.1935	0.2725	0.0742	0.5663	0.6014	6

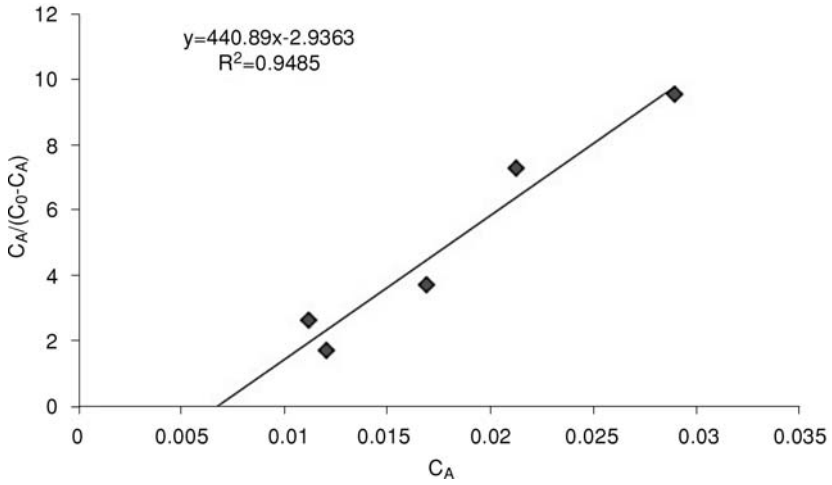

Figure 1. Langmuir adsorption isotherm for chloramphenicol

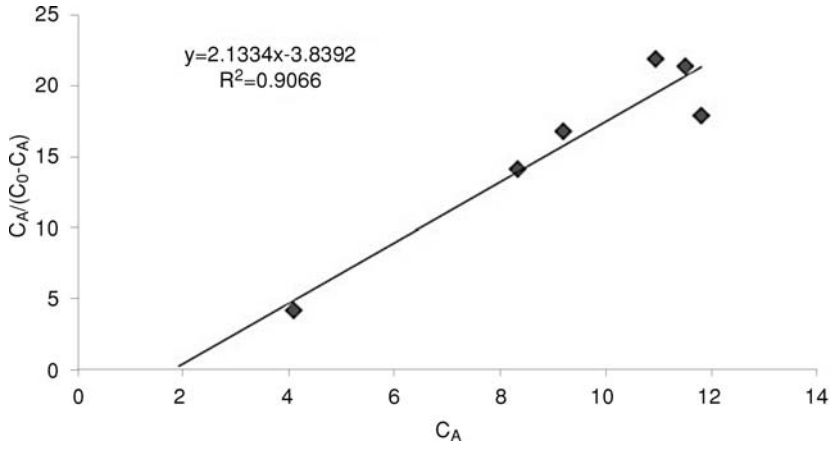

Figure 2. Langmuir adsorption isotherm for gentamicin

The aim of this study was to test the adsorption capacity of selected antibiotics (chloramphenicol, gentamicin, ceftazidime) on the surface of silica nanoparticles and to investigate the desorption process of adsorbed substances.

EXPERIMENTAL

Materials and methods

In this study we used silica nanoparticles size 150 nm obtained at the Institute of Materials Science and Applied Mechanics, University of Technology, Faculty of Mechanical Engineering. The silica nanoparticles were synthesized using TEOS as a main substrate in semi-batch process of the sol-gel method. Size of the nanoparticles was confirmed by DLS method using Zetasizer Nano ZS.

In the experiments we used the following substances:

- chloramphenicol – Detreomycyna (company: Polfa Kraków)
- ceftazidime – Biotum (company: Bioton)
- gentamicin sulfate – Gentamycin (company: Pharma Cosmetic).

Stock solutions of test substances were prepared by dissolving them in purified water. In the

case of poorly soluble chloramphenicol dissolution the process was carried out with heating. All tests were carried out spectrophotometrically using a UV-VIS spectrophotometer (Jasco V-650).

Adsorption study – was conducted in polyvinyl trays. Six concentrations were made for each substance, and for each concentration there were 6 samples (repetitions). 1 mg of silica nanoparticles was weighed on an analytical balance, and placed into the cuvette. Then 2 mL of the drug solution at the specified concentration were added to the cuvette with nanoparticles. The whole was shaken and allowed to stand for 30 min for the adsorption process to occur (during the first 30 min the adsorption process is most intensive). After this time the samples were centrifuged for about 3 min at a speed of 3000 rev/min, to sediment nanoparticles to the bottom of the cuvettes so as not to hinder the measurement. Then the absorbance of the solutions was measured after adsorption with a suitable substance for a particular wavelength. As a reference pure water was used with 1 mg of silica nanoparticles. The concentrations of the solutions were calculated from the linear regression equation obtained at the time of plotting the standard curves for each substance. Amounts of adsorbed substances were calculated from the differences in the concentrations of the solution before adsorption and after adsorption. Knowing the concentration of the solution after adsorption and the amount of a substance that has been adsorbed, it was possible to determine the Langmuir and Freundlich adsorption isotherms.

Desorption study – the sample remaining after the adsorption process was used to study the desorption. In each cuvette, gently, so as not to give rise to precipitate silica nanoparticles, half (1 mL) of the supernatant solution of nanoparticles was collected with an automatic pipette. To each cuvette was added 1 mL of purified water. The whole was shaken to re-excite and mix the suspension of nanoparticles. Due to the dilution of the solution there was imbalance of adsorption-desorption and the adsorbed drug began to be released from the surface of the nanoparticles. Measuring the amount of the released substance was performed after 30 min (after centrifugation of the sample for about 3 min), and then on successive 3-6 days until the end of the process. Measurements were performed in a UV-VIS spectrophotometer (Jasco) at the appropriate wavelength using, as a reference, water containing 1 mg of nanoparticles.

RESULTS AND DISCUSSION

The study showed that chloramphenicol is adsorbed onto the surface of silica nanoparticles. The percentage of adsorbed substances depended on the concentration of the initial solution containing nanoparticles, and values ranged from 10.97% to 36.40%.

In order to check the type of adsorption for chloramphenicol, adsorption isotherms were plotted. The results of adsorption of chloramphenicol on the surface of silica nanoparticles are shown in Table 2 and the results of the statistical analysis are shown in Table 3. The analysis showed that the Langmuir isotherm p-value was < 0.05. The course

Table 4. Average values of the desorption from the surface of chloramphenicol silica nanoparticles endpoint desorption. (Negative desorption results may result from the detection limit of antibiotic concentration in the spectrophotometric method used). (The results in the tables have been rounded to the fourth decimal place).

Initial concentration of the solution [mg/mL]	0.0325	0.0245	0.0216	0.0190	0.0154	0.0063
Average amount of drug desorbed from 6 measurements [mg]	0.0005	0.0003	-0.0007	0.0006	-0.0011	-0.0001
Average % desorbed from 6 measurements	14.8148	9.3137	-15.6028	7.9710	-32.8125	-5.1282

Table 5. Results of gentamicin average adsorption on the surface of silica nanoparticles. (The results in the tables have been rounded to the fourth decimal place).

Initial concentration of the solution [mg/mL]	12.6213	12.067	11.6798	9.9309	9.0723	5.2404
Average amount of drug adsorbed from 6 measurements [mg]	0.5336	0.3406	0.7330	0.7343	0.7478	1.1542
% Average of 6 measurements adsorbed	4.2274	2.8224	6.2758	7.3938	8.2430	22.0254

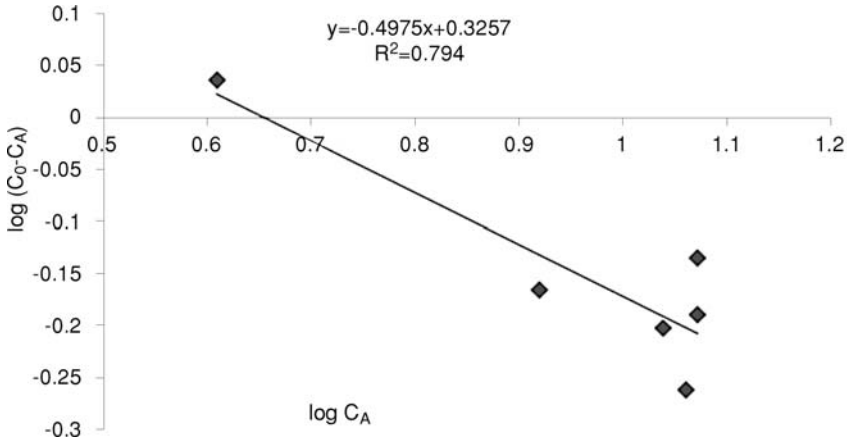

Figure 3. Freundlich adsorption isotherm for gentamicin

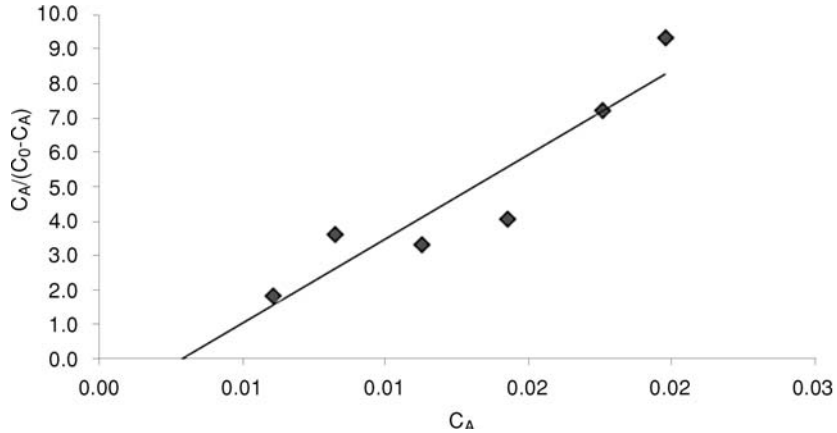

Figure 4. Langmuir adsorption isotherm for ceftazidime

of the Langmuir adsorption isotherm is shown in Figure 1. The possibility to plot the isotherm leads to the conclusion that the process of chloramphenicol adherence on the surface of nanoparticles is chemisorption.

Studies have shown that chloramphenicol desorption from the surface of silica nanoparticles practically does not occur. No desorption process also confirms that chloramphenicol is primarily chemisorbed on the surface of nanoparticles, and the amount of physically adsorbed drug is negligible and the results are shown in Table 4.

The study showed that gentamicin is adsorbed on the surface of silica nanoparticles. The average amounts of the drug which have been adsorbed are shown in Table 5. Percentage of adsorbed substances depended on the concentration of the initial solution containing nanoparticles, and values ranged between 2.82% and 22.03%.

In order to determine the type of gentamicin adsorption, the adsorption isotherms were plotted. The results of statistical analysis are shown in Table 6. The analysis showed that for both isotherms the confidence level p-value is less than 0.05.

The course of the Langmuir isotherm is shown in Figure 2, the Freundlich isotherm in Figure 3. The possibility to plot the two isotherms leads to the conclusion that the process of gentamicin adsorption on the surface of silica nanoparticles is both physical and chemical adsorption.

Table 6. Statistical analysis of the correlation values used to plot the Langmuir adsorption isotherm (L) and Freundlich (F) for gentamicin. (The results in the tables have been rounded to the fourth decimal place).

		Average	Std. stand.	r	r^2	t-test	p	N
L	C_A [mg/mL]	9.3134	2.9007					
	$C_{0\text{-}C\,A}$ [mg]	16.0297	6.4992	0.9522	0.9066	6.2319	0.0034	6
F	Log C_A	0.9669	0.1855					
	Log ($C_{0\text{-}C\,A}$)	-0.2472	0.1845	-0.8538	0.7290	-3.2800	0.0305	6

Table 7. Average values of the desorption from the surface of gentamicin silica nanoparticles endpoint desorption. (Negative desorption results may result from the detection limit of antibiotic concentration in the spectrophotometric method used). (The results in the tables have been rounded to the fourth decimal place).

Initial concentration of the solution [mg/mL]	12.6213	12.067	11.6798	9.9309	9.0723	5.2404
Average amount of drug desorbed from 6 measurements [mg]	-0.4216	-0.3319	0.0092	0.0949	-0.1309	-0.5387
Average % desorbed from 6 measurements	-79.0105	-97.4359	1.2574	12.9284	-17.5002	-46.6730

Table 8. Average values of surface adsorption of ceftazidime silica nanoparticles. (The results in the tables have been rounded to the fourth decimal place).

Initial concentration of the solution [mg/mL]	0.0229	0.0205	0.0179	0.0154	0.0111	0.0097
Average amount of drug adsorbed from 6 measurements [mg]	0.0031	0.0022	0.0036	0.0041	0.0024	0.0036
% Average of 6 measurements adsorbed	13.6099	10.5691	20.2048	26.7316	21.7718	37.4570

Table 9. Statistical analysis of the correlation values used to plot the Langmuir adsorption isotherm (L) and Freundlich (F) for ceftazidime. (The results in the tables have been rounded to the fourth decimal place).

		Average	Std. stand.	r	r^2	t-test	p	N
L	C_A [mg/mL]	0.0129	0.0053					
	$C_{0\text{-}C\,A}$ [mg]	4.8912	2.7950	0.9317	0.8681	5.1316	0.0068	6
F	Log C_A	1.9281	0.1992					
	Log ($C_{0\text{-}C\,A}$)	2.5032	0.0719	-0.3342	0.1117	-0.7091	0.5174	6

Table 10. Mean values of ceftazidime desorption from the surface of silica nanoparticles endpoint desorption. (The results in the tables have been rounded to the fourth decimal place).

Initial concentration of the solution [mg/mL]	0.0229	0.0205	0.0179	0.0154	0.0111	0.0097
Average amount of drug desorbed from 6 measurements [mg]	0.0010	0.0012	0.0014	0.0014	0.0016	0.0017
Average % desorbed from 6 measurements	30.6452	52.2727	39.8148	33.3333	65.2778	48.1481

The desorption process of gentamicin from the surface of the nanoparticles practically does not occur. No desorption of gentamicin from nanoparticles shown in Table 7 suggests that it is largely chemisorbed on it, and the amount of drug which is physically adsorbed is very low.

The results revealed that ceftazidime is a medicine that is best adsorbed on the surface of silica nanoparticles. The mean values of the adsorption of ceftazidime are shown in Table 8. Percentage of drug adsorbed depends on the initial concentration of the solution, varying between the values of 10.57% and 37.46%.

In order to check the type of adsorption of ceftazidime, the Freundlich and Langmuir adsorption isotherms were plotted. The results of statistical analysis of data are shown in Table 9.

Statistical analysis showed that the Langmuir isotherm confidence level is less than 0.05. The Langmuir isotherm is shown in Figure 4. The possibility to plot the isotherm leads to the conclusion that ceftazidime is chemisorbed on the surface of silica nanoparticles.

Ceftazidime was the only one of the study drugs to undergo a process of desorption from the surface of silica nanoparticles in an inert environment. The amount of drug which has been desorbed decreased with increasing concentration of the initial solution and ranged from 1 to 1.7 mg, which represents from 30.65% to 65.28% of the amount adsorbed. Such a high percentage of desorption may indicate that the drug is, however, somewhat physically adsorbed. The results of the desorption process are shown in Table 10. The desorption process in the case of the drug is very long, and the end of the desorption occurs after 144 h and does not depend on the initial concentration of the solution. The stability of the ceftazidime aqueous solution was confirmed by spectrophotometric analysis of the substance spectrum.

All tested drugs underwent adsorption on the surface of silica nanoparticles. The most strongly adsorbed was ceftazidime. The highest percentage of the adsorbed drug was at the lowest initial concentration of the drug solution and was 37.5%. Chloramphenicol adsorbed slightly less than ceftazidime, and gentamicin adsorbed the least, and the highest percentage of drug absorbed was slightly more than 22%. The strong adsorption of ceftazidime is associated with the complex structure of the drug. Among the studied molecules, ceftazidime contains many double bonds between the carbon atoms. This allows the production of a large number of binding π complexes between nanoparticles and the drug molecule. Moreover, in the ceftazidime molecule, there are numerous carbonyl and amino groups which may participate in hydrogen bond formation. Interpretation of the level of adsorption is only an attempt to explain this phenomenon and is based on the concept of some kind π bond formation between the drug particles and the free electron pairs of the oxygen atoms of the hydroxyl substituents located on the surface of silica nanoparticles. There is reduced adsorption of chloramphenicol due to its simpler structure. The chloramphenicol molecule is much smaller; it has small double bond groups and is much less likely to form hydrogen bonds. The weakest of the tested, adsorbed substances is gentamicin. The drug molecule has no double bond, which cannot produce a π bond, and it is mainly due to the adsorption of a number of groups having a hydrogen bond to form (hydroxy, amino, carbonyl).

CONCLUSIONS

Analysis of the results of the study led to the following conclusions:

- All tested drugs (i.e., chloramphenicol, gentamicin and ceftazidime) adsorbed on the surface of silica nanoparticles.
- The amount of adsorbed substance depends primarily on its structure. Ceftazidime, as the compound with the highest number of double bonds, and a large number of groups to form hydrogen bonds (carbonyl groups, amino groups), adsorbed to the greatest extent.
- The precise adsorption for each of the drugs is difficult to establish. The results indicate that in the case of chloramphenicol it is essentially a process of chemisorption, and for gentamicin and ceftazidime both physical and chemical adsorption, without there being any clearly defined relationship between the two processes.
- The drug that underwent the greatest desorption from the surface of nanoparticles was ceftazidime. Gentamicin and chloramphenicol strongly bound to the surface of nanoparticles and desorbed at neutral pH.
- The purpose of the nanoparticles as drug carriers is to obtain controlled and prolonged exposure to the drug. The current state of knowledge indicates that the possibility of connection of antibiotics to the surface of silica nanoparticles may increase the antibacterial potency, as demonstrated for example of ciprofloxacin (15, 16). Studies on the desorption process showed that the drugs are gradually desorbed in time and nanoparticles of

the adsorbed active substance may be a form of the drug reservoir in the body. Despite the unknown toxicity of the silica nanoparticles to tissues, there is a real possibility of using them as a new carrier for antibiotics. Silica nanoparticles as a carrier are eliminated from the body by the kidneys due to passive diffusion through the glomerular filtration membrane pores.

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