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PHYSICOCHEMICAL ASPECTS OF THERAPEUTIC EFFECT OF ENTEROSORBENTS (THEORETICAL RESEARCH)

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Active promotion of enterosorbents to the market outruns thorough study of the mechanisms of their therapeutic effect. The consumers and even many specialists have a simplified view of the only role of the enterosorbents to fix and remove toxins, that is, act as a "cleaner" of the body.

The aim of this paper is to reveal the importance of physicochemical factors for the therapeutic action of enterosorbents. These factors include: (i) electrostatic charge of sorbent surface; (ii) pore size; (iii) accessible area of surface; (iv) hydrophilic-hydrophobic balance of surface; (v) ion exchange properties; (vi) capability to structure water. Mentioned factors can be estimated quantitatively using such methods as electrophoresis, gas chromatography, photon correlation and ^1H NMR spectroscopy, volumetric analysis, etc. However, in pharmaceutical practice, it is more convenient to characterize the enterosorbent by its capability to adsorb some test substances. To examine the above factors, we use oppositely charged dyes methylene blue and congo red, ions of Zn^{2+}, gelatin, phenol and amino acid tryptophan. By the help of this approach we have characterized various types of charcoal, nanosized fumed silica (Atoxil), porous Syloid® 244FP, hydrophobic Aerosil® R972, silica gel, Enterosgel, fumed alumina, Smecta®, zeolites, kaolin, any derivatives of cellulose, lignin and other materials. To study the interaction of enterosorbents with the intestinal mucosa, a gel of eye vitreous humor was used as a model.

As a result, we concluded that nanosized silica might be considered first of all as enveloping agent, the main mechanism of action of which is interaction with glycoproteins of the intestinal mucosa. Consequently, two therapeutic effects are realized: (1) difficulty forms for diffusion of pathogenic substances through the mucosa that leads to decrease in their absorption; (2) antidiarrheal effect due to protecting mucosal receptors from the adhesion of microorganisms and impact of microbial toxins. Taking into account that the intestinal mucosa throughout its extent, in the pH range from 6.0 to 9.0, is negatively charged, this interaction for silica occurs with the overcoming of electrostatic repulsion. Therefore, the enveloping power of silica is less than that of alumina containing preparations which in the intestine have a positive charge. Generally speaking, the absorbing mechanism of healing action can only be applied to highly porous sorbents such as charcoal, zeolites, silica gel, Syloid® 244FP, etc.

Keywords*: enterosorbents, therapeutic effect, silica, alumina, intestinal mucosa, pH, electrostatic charge*

INTRODUCTION

In connection with the wide spread of the enterosorption as therapeutic method, the actual task is to study the molecular mechanisms of action of enterosorbents. The general population and even many specialists have a simplified view of the only role of the enterosorbents to fix and remove toxins, that is, act as a «cleaner» of the body.

To date, based on the chemical nature, enetrosorbents can be classified as follows:

- carbon sorbents obtained from natural or synthetic row materials: charcoal, Sorbex®;
- natural and synthetic aluminosilicates, glue minerals: kaolin, Smecta®;
- synthetic silicon containing sorbents (organosiloxanes, aerosils): Dimethicone, Enterosgel, nanosized fumed silica (Atoxil);
- biopolymers, including natural organic fibers («food fibers»): microcrystalline cellulose, chitosan, pectin, Laminarin, lignin;
- synthetic polymers of organic origin: Polyvinylpyrrolidone, Cholestiramine;
- complex preparations: White charcoal®.

From the structural point of view enterosorbents can be divided into the next types:

- porous: charcoal, silica gel, Sorbex®, Syloid® 244FP;
- non-porous, highly disperse: nanosized silica (Atoxil), kaolin;
- laminate: Smecta®;
- fibrous: microcrystalline cellulose, lignin.

V.G. Nikolaev [1, 2] defines 14 mechanisms of healing effect of enterosorbents which are represented by four directions (Fig. 1):

i ii iii iv

Fig. 1. Pictograms that reflect the mechanisms of healing effect of enterosorbents: i) adsorption of toxins, metabolites, microorganisms; ii) protection of mucosa; iii) interaction with chyme and iv) specific effects: antimicrobial, catalytic, source of microelements, *etc.*

An exceptionally important role for the realization of the therapeutic effect of enterosorbents is their physicochemical features which can be estimated quantitatively using modern instrumental methods, such as electrophoresis, gas chromatography, photon correlation and ^{1}H NMR spectroscopy, *etc.* However, in pharmaceutical practice, it is very effective to characterize enterosorbents by the capability to adsorb some test substances.

The aim of this paper is to reveal the physicochemical aspects of the healing effect of enterosorbents, the example being adsorption of various test substances, and to develop the model of behavior of Si- and Al-containing enterosorbents in the gastrointestinal tract. In creating this model, we proceeded from the leading role of electrostatic effects in the mechanism of therapeutic action of enterosorbents.

EXPERIMENTAL BACKGROUND

For a theoretical research, we used our own results on the adsorption by various materials of the test substances among them differently charged dyes methylene blue and congo red, zinc ions, gelatin, amino acid tryptophan and phenol. The results were received during 2006–2017. Characteristics of materials, both registered enterosorbents and laboratory samples, are listed in the Table 1.

The specific surface area of the materials was determined by the methods of low-temperature adsorption-desorption of nitrogen or thermal desorption of argon.

The adsorption experiment was carried out according to the standard procedure [3]. To the exact weight of the material, the determined volume of the test solution was added and moderately shaken for 1–4 hours. After that, it was centrifuged and the equilibrium concentration of the test substance was determined in a centrifugate by the corresponding analytical method. The value of adsorption in mg/g was calculated from the difference in the initial and equilibrium concentrations. Some of the results given in the table were obtained by building an adsorption isotherm, with the maximum observed adsorption value. The other part of the results is obtained through the measurement of the adsorption «at one point», this approach is acceptable for quality control. Thus, the table gives only a general picture, strictly comparable can be only the results obtained in one particular study, that is, under the same conditions.

Since work with native mucosa is difficult, we used as its model an ophthalmic vitreous humor, close to mucosa in terms of chemical composition, consistency and charge of the polymer matrix [4]. Vitreous humor contains 99 % water, its main component is hyaluronic acid, belonging to the class of heteropolysaccharides. A large number of $–COO^{–}$ groups imparts a negative charge to the hyaluronic acid molecule and to the vitreous humor as a whole. The protein component of the vitreous humor is represented mainly by collagen fibers [5]. Like mucosa, the vitreous humor acts as a selective barrier for small molecules [6]. A standardized vitreous preparation obtained from the eyes of cattle was used in the study [4], its pH is 8.5. Mixtures of vitreous humor with water with increasing biosubstrate content were added to the exact weights of fumed silica or alumina and shaken for 1 hour. After that, it was centrifuged and the equilibrium concentration of hyaluronic acid and protein was determined in a centrifugate. The value of adsorption in mg/m^2 was calculated from the difference in the initial and equilibrium concentrations, then the results

were presented as dependence of the adsorption on the equilibrium concentration.

THEORETICAL RESEARCH

Adsorption of test substances. The data presented in Table 1 show the leading role of electrostatic effect in the interaction of the examined materials with the test substances. First of all it concerns materials with ionogenic functional groups on the surface, for example, Si- and Al-containing sorbents. Thus, the isoelectric point (IEP) of SiO_2 is at pH 2.2 [7], and of pyrogenic Al_2O_3 is at pH 9.8 [8], so in a neutral aqueous solution the particles of the first material are charged negatively, and those of the second one – positively. Accordingly, alumina does not absorb the equally charged cations of methylene blue, but well absorbs the congo red anions (125 mg/g); for silica A-300 and porous Syloid® 244FP an inverse regularity is observed. In the case of Enterosgel, hydrophobic interaction is added to the electrostatic one, so the difference in adsorption of dyes is negligible. The electrostatic mechanism is inherent for negatively charged cellulose derivatives and zeolites that better adsorb methylene blue compared to congo red. Phenol belongs to weak acids and dissociates significantly only in alkaline medium. At pH 2.0, the phenol molecule is in a non-dissociated state, and at pH 7.5 it forms only a small amount of phenolate ions $C_6H_5O^-$. The benzene core and the –OH group in the structure of phenol give it a capability to interact with hydrophobic and hydrophilic mechanisms, which results in its high affinity to coal sorbents having hydrophobic basal surfaces and hydrophilic groups at the edges of these surfaces. In addition, the small size of the phenol molecule allows it to penetrate into the microporous charcoal. Other materials by sorption of phenol are considerably inferior to charcoal. Comparison of sorption of phenol by silica and Enterosgel shows that more hydrophobic Enterosgel is more active. At pH 7.5, the activity of both sorbents is significantly less than that of pH 2.0, that can be explained by electrostatic repulsion between $Si–O^-$ groups on the surface of sorbents and phenolate anions, which are present in a small amount in a solution at pH 7.5.

For such multi-functional substances as proteins, the electrostatic adsorption mechanism appears together with other mechanisms. For gelatin IEP is observed at pH 4.8–5.0, so at pH 2.0 this protein is charged positively, and at pH 7.0 – negatively. The greatest attraction between the molecules of gelatin and silica surface occurs in the range of pH 2–5, that is between IEP_{SiO_2} and IEP of gelatin. Outside of this range, the protein and the silica surface are charged equally and repulse each other [9], but adsorption, although to a lesser extent, is maintained by other interactions – through hydrogen bonding (in acidic media) and hydrophobic interaction. For completely non-ionogenic Aerosil® R972 and polymethyl-siloxane (PMS), high sorption of gelatin apparently occurs due to hydrophobic interaction.

Such structural factors as the pore size and specific surface area also have a significant effect on the magnitude of sorption. So, gelatin is practically not absorbed by charcoal and silica gel that is due to the protein molecules are too large to penetrate into the micropores of these materials with a developed internal surface. Strongly violates this regularity microporous zeolite NaX well absorbing gelatin at pH 7.5. The behavior of smectite, which has a laminate structure, is characterized by essential features. The high adsorption of methylene blue (about 600 mg/g), congo red and gelatin is due to the fact that smectite swells in an aqueous medium and the distance between atomic layers becomes sufficient for penetration of sorbate molecules; accordingly, size of the available surface significantly increases [10]. Close to smectite in composition but incapable of swelling, kaolin demonstrates essentially lower adsorption of dyes and gelatin.

The study of the adsorption of Zn^{2+} ions provides useful information on pore sizes and on the capability of the material to exchange ions. Thus, the feature of zeolites is the presence in their structure of channels of precisely defined size, 0.9 nm for NaX zeolite and 0.4 nm for NaA [11]. The size of the Zn^{2+} ion, according to various authors, ranges from 0.06 to 0.08 nm [12], which is considerably smaller, that enables active absorption and exchange for cations located in the channels. Disaccordance between the extremally high absorbtion of Zn^{2+} with zeolites and small value of their S (only 7.7 and 14.9 m^2/g, respectively), possibly due to the whole area of surface can not be measured exactly with low-temperature adsorption–desorption of nitrogen, so in this case absorption of Zn^{2+} is considered as a more convenient method for this aim.

Table 1. Probing of sorbents with test substances

Sorbent	Features	*S*, m^2/g	Adsorption, mg/g					
			Methylene Blue	Congo Red	Ions of Zn^{2+}	Gelatin	Trypto-phan	Phenol
Fumed silica A-300	Non-porous, (–) charged	300[c,f]	11.3[a] 14.1[b] 23.0[c] 73[d] 36.3[f]	0[a] 1.79[b] <2.0[c]	0.136[a] 0.078[b]	300[a] 344[b] 337[d] 276[f]	<0[b]	48.6[f] (pH 2.0) 0[f] (pH 7.5)
Aerosil® R972 Pharma	Non-porous, hydrophobic	130	3.95[b]	8.54[b]	0.052[b]	150[b]	1,76[b]	…
Syloid® 244 FP	Mesoporous, (–) charged	354[g]	17.5[b] 50[g]	1.51[b] <6[g]	0.234[b] 2.3[g]	317[b]	<0[b]	…
Enterosgel	Hydrophilic-hydrophobic, (–) charged	…	7.24[b] 18.0[c] 26.2[f]	26.4[b] 17.5[c]	0.072[b]	439[b] 245[d]	1,36[b]	55.6[f] (pH 2.0) 9[f] (pH 7.5)
Silica gel	Microporous, (–) charged	…	1.47[b]	1.24[b]	0.29[a] 0.241[b]	0[a] <0[b]	<0[b]	…
Polymethyl-siloxane	Microporous, hydrophobic	494[c] 520[f]	3.38[b]	15.3[b]	0.044[b]	102[b]	<0[b]	…
Smectite, obtained by washing/ drying of Smecta®	Laminate, (–) charged	25[c] 31[f] 75.7[g]	600[c] 125[e] 430[g]	45.0[c] 125[f] 100[g]	2.5[g]	143[e] 164[f] (pH 2.0) 113[f] (pH 7.5)	…	5.7[e]
Kaolin	Non-porous, (–) charged	13[c] 10[f] 11.6[g] 18[e]	13.0[c] 37.3[e] 15[g]	4.5[c] <6[g]	2.2[g]	37[e]	…	4.8[e]
Fumed alumina	Non-porous, (+) charged	110[c]	0[c]	125[c]	…	100	…	
Zeolite NaX	Microporous	7.7[f]	63.6[f] 7[g]	<6[g]	>25[g]	57.5[f] (pH 2.0) 108[f] (pH 7.5)	…	5.9[f] (pH 2.0) 5.6[f] (pH 7.5)
Zeolite NaY	Microporous	16.4[f]	26.2[f]	…	…	26[f] (pH 2.0) <10[f] (pH 7.5)	…	4.7[f] (pH 2.0) 5.6[f] (pH 7.5)
Zeolite NaA-TK-1173	Microporous,	14.9[g]	13[g]	<6[g]	>15[g]		…	
Charcoal	Microporous, hydrophilic-hydrophobic	920[f]	190[d] 92.5[f]	97[g]	…	0[d] 0[f]	…	79.8[f] (pH 2.0) 124[f] (pH 7.5)
Enterosor-bent SCN	Microporous, hydrophilic-hydrophobic	2850[h]	580[h]	112[h]	1[g]	…	…	…
Microcrystal-line cellulose	Fibrous	…	4.6[a] 22.8[d]	14.9[a]	0.192[a]	0[a] 0[d]	…	…
Croscar-melose-Na	Fibrous, (–) charged	…	18.6[a]	5.6[a]	0.284	0[a]	…	…
Carboxyme-thylcellulose	Fibrous, (–) charged	…	12.3[a]	5.5[a]	…	0[a]	…	…
Cellulose	Fibrous	…	15.4[a]	23.8[a]	0.154[a]	0[a]	…	…

Notes: *a* – by [15]; *b* – by graduate thesis of K. Gradzion; *c* – by [13]; *d* – by [16]; *e* – by [19]; *f* – by [14]; *g* – by [17]; *h* – by [18]. *S* for smectite is given without additional surface, which is formed after swelling in water

It is instructive to compare the adsorption of Zn^{2+} ions and gelatin by Si-containing sorbents. Silica gel due to the microporous structure actively absorbs Zn^{2+} ions, but does not adsorb gelatin at all. At the same time, large-porous Syloid® 244FP retains a high adsorption capacity with respect to both test substances.

The water-soluble amino acid tryptophan, which has a bulk aromatic fragment in its structure, is not adsorbed by hydrophilic surfaces, but interacts with the hydrophobic Aerosil® R972 Pharma and hydrophilic-hydrophobic Enterosgel. Moreover, for hydrophilic materials, there is a significant negative adsorption of the amino acid, which can be regarded as a preferred adsorption of water. It is difficult, however, to explain the lack of adsorption of tryptophan by hydrophobic PMS.

Summing up, on the basis of numerous observations, it is possible to emphasize the physicochemical factors of the therapeutic action of enterosorbents as it is presented in Table 2.

Table 2. Physicochemical factors of healing effect of enterosorbents and approaches for their examination

Factor	Approach		Typically examined materials
	Using instrumental method	Using test substances	
Electrostatic charge of sorbent's surface	Electrophoresis	Methylene blue (+), congo red (–)	Fumed silica A-300 (–), fumed alumina (+)
Pore size/volume	Capillary flow porometry	Ions of Zn^{2+}	Silica gel, zeolites, Syloid® 244FP
Surface area	Gas chromatography	Gelatin (for non- and macroporous sorbents)	Fumed silica A-300, Enterosgel, Syloid® 244FP
Hydrophilic-hydrophobic balance of surface	Adsorption of water/hexane	Tryptophan, phenol	Enterosgel, Aerosil® R972 Pharma
Ion exchange properties	Volumetric analysis	Ions of Zn^{2+}	Silica gel, zeolites, smectite
Capability to structure a water	^{1}H NMR spectroscopy	…	Fumed silica A-300, Enterosgel

To speak briefly, cationic dye methylene blue (M.m. 320 g/mol), which simulates positively charged low-molecular substances (alkaloids, histamine, dimedrol, novocaine hydrochloride, promedol, *etc.*) is used to test materials with a negatively charged surface.

Conversely, anionic congo red dye (M.m. 697 g/mol) is used as a test substance for studying the adsorption of negatively charged low- and middle-molecular substances (sodium diclofenac, salicylates, analgin, asparcam, barbituric acid salts, salts of fatty and biliary acids, *etc.*) by materials that carry a positive charge in the solution.

Zinc ions can detect microporosity, as well as the capability of materials to exchange cations located in the porous and interlayer space. Zinc simulates poisoning with «heavy metals»: copper, lead, cadmium, mercury, *etc.*

Diphilic phenol and tryptophan are useful for identifying sorbents capable of binding substances that exhibit hydrophilic-hydrophobic properties in aqueous solution.

The value of gelatin adsorption is well correlated with the surface size of non-porous and macroporous sorbents. Gelatin is used as a test substance which simulates the adsorption of toxins and metabolites of protein nature.

Among the above physicochemical factors, the most important is the electrostatic charge of sorbent's surface, especially in the pH range 6–9, which corresponds to the physiological pH gradient in the intestine throughout its extent, from the duodenum to the large intestine (Fig. 2). This gradient is formed as a result of secretion of neutral and slightly alkaline substances in the upper parts of the small intestine and under the impact of alkaline products of vital activity of the microflora of the large intestine [20]. As is known, the main structural component of the intestinal mucosa is glycoproteins with a molecular weight of about 1 million Da (mucins) that form a hydrogel, in which all

macromolecules are linked to each other by transverse bonds [21]. Since the lateral polysaccharide chains of mucins end up mostly by sialic acid (pK 2.6), the mucosa in the indicated range of pH is negatively charged [22]. This fact will determine the behavior in the intestine of sorbents, for which the electrostatic charge of the surface serves as an essential feature.

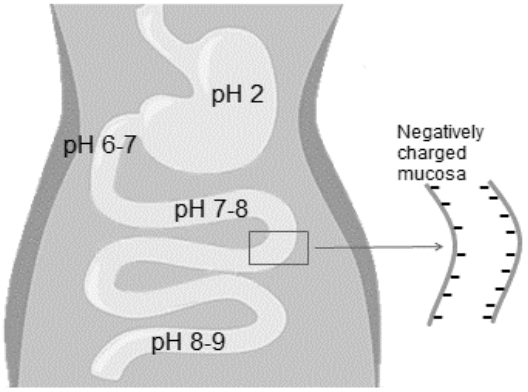

Fig. 2. Normal pH value in different regions of gastrointestinal tract and charge of mucosa

Sorption of components of vitreous humor (model experiment). The adsorption isotherms of the protein of vitreous humor on silica and alumina are presented in Fig. 3. As shown, the experimentally observed maximum value of protein adsorption from native (undiluted) vitreous humor which corresponds to the last point on the curve, is 5.5 times lower on SiO_2 (0.066 mg/m^2) than on Al_2O_3 (0.362 mg/m^2). (When recalculated to mg/g, this difference remains, although it becomes somewhat smaller). This is due to the vitreous humor protein at pH 8.5 occurs in an anionic form, that reduces its adsorption on the surface of silica carrying a significant negative charge ($IEP_{SiO2} = 2.2$), and increases adsorption on Al_2O_3, the surface of which is positively charged ($IEP_{Al2O3} = 9.8$).

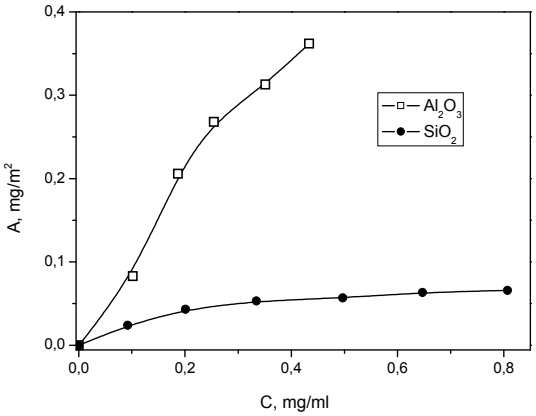

Fig. 3. Adsorption of protein of vitreous humor on fumed silica and alumina [4]

The adsorption curves of hyaluronic acid on the studied oxides have clearly marked maxima, with adsorption on SiO_2 in a maximum (at pH 7) almost 10 times lower than on Al_2O_3 (Fig. 4). As in the case of protein adsorption, this can be explained by the electrostatic attraction of the oppositely charged groups $–COO^–$ of hyaluronic acid and the alumina surface and, accordingly, by repulsion of these groups from the equally charged silica surface. A sharp decrease in adsorption with increasing of vitreous humor concentration can be caused by a growth of pH in the medium, since the last points on the curves were obtained for adsorption from an undiluted vitreous humor having a pH of about 8.5. At a given pH value, the negative charge of the silica surface becomes sufficiently large, and for aluminum oxide it approaches to IEP, that counteracts the adsorption of the polyanion of hyaluronic acid. Another reason for the appearance of maxima on the curves may be due to the preferential sorption from the native vitreous body of water, rather than of hyaluronic acid.

Comparing the behavior of silica and alumina in a model experiment, we ask ourselves: should classify nanosized silica as enterosorbent or it is rather an enveloping (or mucoadhesive) agent, the main mechanism of action of which is interaction with components of the intestinal mucosa such as glycosamino-glycans, glycoproteins, *etc*.? This alternative is shown schematically in Fig. 5.

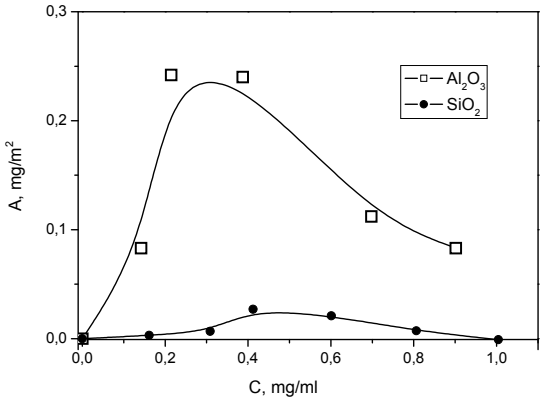

Fig. 4. Adsorption of hyaluronic acid of vitreous humor on fumed silica and alumina [4]

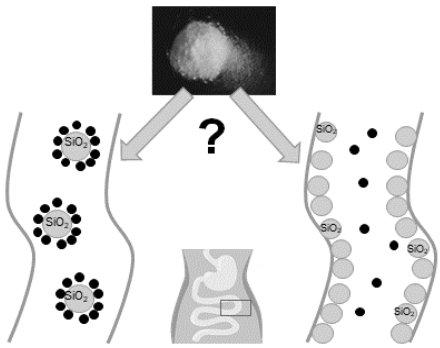

Fig. 5. Nanosized silica: enterosorbent or mucoadhesive?

Based on the obtained results, we are inclined to the second option. There is one more circumstance: silica nanoparticles are too small to sorb on themselves large-molecule toxins, it is easier for them to adsorb on the extended surface, which is the surface of the mucosa. Total surface area of the small intestine is about 300 m^2 [23] which is commensurate with the surface area of 1 gram of highly disperse silica. Consequently, this amount of silica which is its minimal therapeutic dose is sufficient to completely envelop this part of the intestina. Another structural feature approximates silica to mucoadhesives: it is the saturation of its surface with hydroxyl groups, which are capable to form numerous hydrogen bonds with the macromolecules of the mucosa. If we admit the mucoadhesive mechanism as the main for silica, then two therapeutic effects are realized: (1) difficulty forms for diffusion of pathogenic agents through the mucosa that leads to decrease of their absorption; (2) antidiarrheal effect due to protecting mucosal receptors from the adhesion of pathogenic microorganisms and impact of microbial toxins.

Taking into account that the intestinal mucosa throughout its extent, in the pH range from 6.0 to 9.0, is negatively charged (Fig. 2), the interaction with equally charged silica occurs with the overcoming of electrostatic repulsion. Therefore, the enveloping power of silica is less than that of alumina containing preparations which in the intestine have a positive charge.

CONCLUSION

Physicochemical factors of the therapeutic action of enterosorbents include: (i) electrostatic charge of sorbent's surface; (ii) pore size and volume; (iii) accessible area of surface; (iv) hydrophilic-hydrophobic balance of surface; (v) ion exchange properties; (vi) capability to structure a water. To estimate the impact of these factors a set of instrumental and adsorptive methods were proposed.

Surface charge of Si- and Al-containing enterosorbents as well as the charge of mucosa are dependent on the value of intestinal pH. Thus, pH is considered as the main factor which regulates the behavior of these enterosorbents in the gastrointestinal tract.

The really adsorbing mechanism can only be applied to highly porous sorbents (charcoal, zeolites, silica gel, Syloid® 244 FP). Nanosized non-porous silica (Atoxil) rather belongs to enveloping preparations. The enveloping power of nanosized silica is less than that of alumina containing preparations (fumed alumina, Smecta®, Almagel®, *etc.*).

Фізико-хімічний аспект терапевтичної дії ентеросорбентів (теоретичне дослідження)

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Активне просування ентеросорбентів на ринок випереджає детальне вивчення механізмів їхньої лікувальної дії. У споживачів і навіть серед спеціалістів популярністю користується спрощена думка про те, що ентеросорбенти лише зв'язують і видаляють токсини, виконуючи функцію очистки організму.

Мета цієї статті – продемонструвати важливість фізико-хімічних чинників для прояву терапевтичної активності ентеросорбентів. До цих чинників належать: (1) електростатичний заряд поверхні сорбента; (2) розмір пор; (3) розмір доступної поверхні; (4) гідрофільно-гідрофобний баланс поверхні; (5) йонообмінні властивості; (6) здатність до структуризації води. Зазначені чинники можна кількісно оцінити, застосовуючи такі методи, як електрофорез, газова хроматографія, методи лазерної кореляційної та ^{1}H ЯМР спектроскопії, об'ємний аналіз та ін. Разом з тим, у фармацевтичній практиці зручніше характеризувати ентеросорбент за здатністю адсорбувати певні тестові речовини. Для оцінки вищезазначених чинників ми використовуємо різнозаряджені барвники метиленовий синій і конго червоний, йони Zn^{2+}, желатину, фенол та амінокислоту триптофан. За допомогою цього підходу ми охарактеризували різні типи активованого вугілля, нанорозмірний пірогенний кремнезем (Атоксіл), пористий Syloid® 244FP, гідрофобний Aerosil® R972, силікагель, Ентеросгель, пірогенний оксид алюмінію, Смекту®, цеоліти, каолін, різноманітні похідні целюлози, лігнін та інші матеріали. З метою дослідження взаємодії ентеросорбентів зі слизовою оболонкою кишечника як модельний об'єкт було використано препарат склоподібного тіла ока.

У результаті ми дійшли висновку, що нанорозмірний кремнезем доцільно розглядати насамперед як обволікаючий засіб, основним механізмом дії якого є взаємодія з глікопротеїнами слизової кишечника. Як наслідок, реалізуються два лікувальних ефекти: (1) утворюється перешкода для дифузії патогенних речовин крізь слизову, що знижує іхню абсорбцію; (2) антидіарейний ефект завдяки захисту рецепторів слизової від адгезії мікроорганзмів та впливу мікробних токсинів. Враховуючи, що слизова кишечника вздовж усієї його довжини, в діапазоні pH від 6.0 до 9.0, заряджена негативно, така взаємодія для кремнезему має відбуватися з подоланням електростатичного відштовхування. Тобто обволікаюча здатність кремнезему буде слабшою, ніж у препаратів на основі оксиду алюмінію, які в кишечнику заряджені позитивно. Загалом, поглинаючий механізм як основний для прояву лікувальної дії може бути застосований лише у разі високопористих сорбентів: активованого вугілля, цеолітів, силікагелю, Syloid® 244FP тощо.

***Ключові слова**: ентеросорбент, терапевтична дія, кремнезем, оксид алюмінію, слизова кишечника, pH, електростатичний заряд*

Физико-химический аспект терапевтического действия энтеросорбентов (теоретическое исследование)

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Активное продвижение энтеросорбентов на рынок опережает детальное изучение механизмов их лечебного действия. Среди потребителей и даже у многих специалистов бытует упрощенное представление о том, что энтеросорбенты лишь связывают и выводят токсины, выполняя функцию очистки организма.

Цель данной статьи – продемонстрировать важность физико-химических факторов для проявления терапевтической активности энтеросорбентов. К таким факторам относятся: (1) электростатический заряд поверхности сорбента; (2) размер пор; (3) площадь доступной поверхности; (4) гидрофильно-

гидрофобный баланс поверхности; (5) ионообменные свойства; (6) способность структурировать воду. Приведенные факторы можно количественно оценить с применением таких методов, как электрофорез, газовая хроматография, методы лазерной корреляционной и ^{1}H ЯМР спектроскопии, объемный анализ и др. Однако, в фармацевтической практике удобнее характеризовать энтеросорбент по способности адсорбировать те или иные тест-вещества. Для оценки вышеназванных факторов мы используем разнозаряженные красители метиленовый синий и конго красный, ионы Zn^{2+}, желатин, фенол и аминокислоту триптофан. С помощью данного подхода ми охарактеризовали разные типы активированного угля, наноразмерный пирогенный кремнезем (Атоксил), пористый Syloid® 244FP, гидрофобный Aerosil® R972, силикагель, Энтеросгель, пирогенный оксид алюминия, Смекту®, цеолиты, каолин, разнообразные производные целлюлозы, лигнин и другие материалы. С целью исследования взаимодействия энтеросорбентов со слизистой оболочкой кишечника в качестве модельного объекта был использован препарат стекловидного тела глаза.

В результате мы пришли к выводу, что наноразмерный кремнезем целесообразно рассматривать прежде всего как обволакивающее средство, основным механизмом действия которого является взаимодействие с гликопротеинами слизистой кишечника. Как следствие, реализуются два лечебных эффекта: (1) образуется препятствие для диффузии патогенных веществ через слизистую, что снижает их абсорбцию; (2) антидиарейный эффект благодаря защите рецепторов слизистой от адгезии микроорганизмов и влияния микробных токсинов. Принимая во внимание, что слизистая кишечника на всем его протяжении, в диапазоне pH от 6.0 до 9.0, заряжена отрицательно, такое взаимодействие для кремнезема должно происходить с преодолением электростатического отталкивания. То есть обволакивающая способность у кремнезема будет слабее, чем у препаратов на основе оксида алюминия, которые в кишечнике заряжены положительно. Вообще говоря, абсорбирующий механизм как основной для проявления лечебного действия применим только в случае высокопористых сорбентов: активированного угля, цеолитов, силикагеля, Syloid® 244FP и др.

***Ключевые слова**: энтеросорбент, терапевтическое действие, кремнезем, оксид алюминия, слизистая кишечника, pH, электростатический заряд*

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