ESTUDO DA PLASMASORÇÃO *IN VITRO* DE LIPOPROTEÍNA E PROPRIEDADES FÍSICO-QUÍMICAS DE SORBENTES POLIMÉRICOS COM GRUPOS AMINO SUBSTITUÍDOS**STUDY OF THE *IN VITRO* LIPOPROTEIN PLASMASORPTION AND PHYSICO-CHEMICAL PROPERTIES OF POLYMERIC SORBENTS WITH SUBSTITUTED AMINO GROUPS****ИЗУЧЕНИЕ СОРБЦИИ ЛИПОПРОТЕИНОВ ИЗ ПЛАЗМЫ *IN VITRO* И ФИЗИКО-ХИМИЧЕСКИХ СВОЙСТВ ПОЛИМЕРНЫХ СОРБЕНТОВ С ЗАМЕЩЕННЫМИ АМИНОГРУППАМИ**

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RESUMO

Atualmente, o método de plasmassorção é amplamente utilizado na prática clínica para remover quantidades excessivas de metabólitos que causam várias patologias. No entanto, os plasmasorbentes aplicados muitas vezes podem fornecer vários efeitos colaterais para o paciente, como a coagulação do sangue, a liberação de partículas de poeira e a absorção de componentes úteis do plasma. Além disso, eles podem ser bastante caros. O objetivo do trabalho foi criar plasmasorbentes disponíveis com boa hemocompatibilidade para a adsorção de lipoproteínas do plasma. Foram sintetizados vários trocadores de ânions com grupos de trimetilamina, monoetanolamina e trietanolamina. Para os sorventes obtidos, foram investigadas as propriedades de adsorção e físico-química. Densidade aparente, volume específico no intumescimento, coeficiente de intumescimento em vários solventes (água, etanol, isopropanol, propilenoglicol, acetona) foram determinados e os cálculos teóricos da capacidade total de troca e massa de reticulação e frações molares foram realizados. Verificou-se que o melhor inchaço é alcançado no propilenoglicol. Para os sorventes LP27 e LP29, foram determinadas as capacidades nas frações de triglicerídeos e lipoproteínas e o coeficiente de distribuição dos componentes do perfil lipídico entre as fases sólida e líquida. É mostrado que ambos os sorventes têm boas propriedades de sorção, sendo a amostra LP29 bastante promissora para a extração dos componentes do perfil lipídico. Presume-se que os sorventes desenvolvidos sejam mais baratos que os atualmente utilizados, pois são sintetizados com base na matriz disponível comercialmente. Espera-se que os resultados obtidos sejam úteis para investigações adicionais visando à melhoria da qualidade da moderna tecnologia de plasmassorção.

Palavras-chave: *Extração de LDL e VLDL, sorção de colesterol, aterosclerose, hipercolesterolemia, doenças cardiovasculares.*

ABSTRACT

Currently, the plasmasorption method is widely used in clinical practice to remove excessive amounts of metabolites that cause various pathologies. However, the plasmasorbents applied often can give a number of side effects for the patient, such as the blood clotting, the release of dust particles, and the sorption of useful components from the plasma. Besides that, they can be quite expensive. The aim of the work was to create available plasmasorbents with a good hemocompatibility for the lipoprotein adsorption from the plasma. A number of anion exchangers with groups of trimethylamine, monoethanolamine, and triethanolamine were synthesized. For the sorbents obtained, adsorption and physico-chemical properties were investigated. Bulk

density, specific volume at swelling, the swelling coefficient in various solvents (water, ethanol, isopropanol, propylene glycol, acetone) were determined and the theoretical calculations of total exchange capacity and crosslinking mass and molar fractions were made. It was found that the best swelling is achieved in propylene glycol. For the sorbents LP27 and LP29, the capacities on triglyceride and lipoprotein fractions and the coefficient of distribution of lipid profile components between the solid and liquid phases were determined. It is shown that both sorbents have good sorption properties, the sample LP29 being quite promising for the lipid profile components extraction. The developed sorbents are assumed to be cheaper than currently used ones as they are synthesized on the basis of commercially available matrix. The results obtained are expected to be useful for further investigations aimed at the modern plasmasorption technology quality improvement.

Keywords: *LDL and VLDL extraction, cholesterol sorption, atherosclerosis, hypercholesterolemia, cardiovascular diseases.*

АННОТАЦИЯ

В настоящее время метод плазмасорбции широко используется в клинической практике для удаления избыточного количества метаболитов, вызывающих различные патологии. Однако используемые плазмасорбенты зачастую могут вызывать ряд побочных эффектов, таких как повышение свертываемости крови, выделение частиц пыли и извлечение полезных компонентов из плазмы. Кроме того, они могут быть достаточно дороги. Целью данной работы было создание доступных плазмасорбентов, обладающих хорошей гемосовместимостью, для извлечения липопротеинов. Был синтезирован ряд анионитов с группами триметиламина, моноэтаноламина и триэтаноламина и исследованы их адсорбционные и физико-химические свойства. Определены насыпная плотность, удельный объем при набухании, коэффициенты набухания в различных растворителях (вода, этанол, изopropanol, пропиленгликоль, ацетон), а также рассчитаны теоретические значения полной обменной емкости и массовой и мольной долей сшивающего агента. Показано, что наилучшее набухание достигается при использовании в качестве растворителя пропиленгликоля. Для образцов ЛБ27 и ЛБ29 определены адсорбционные емкости по триглицеридам и фракциям липопротеинов и рассчитаны коэффициенты распределения компонентов между твердой и жидкой фазами. Показано, что оба сорбента имеют хорошие сорбционные свойства. Наиболее перспективным для извлечения компонентов липидного спектра является образец ЛБ29, имеющий достаточно высокие емкости по всем компонентам. Предполагается, что разрабатываемые сорбенты будут дешевле, чем используемые в настоящее время, благодаря использованию для их синтеза доступного промышленного анионита. Полученные результаты могут быть полезны для дальнейших исследований, направленных на улучшение качества и доступности современных плазмасорбционных технологий.

Ключевые слова: *извлечение ЛПНП и ЛПОНП, сорбция холестерина, атеросклероз, гиперхолестеринемия, сердечно-сосудистые заболевания.*

1. INTRODUCTION

The plasmasorption method is widely used in clinical practice for the treatment of pathologies caused by the increased content of certain substances in the blood. In particular, it is prescribed for the treatment of atherosclerosis caused by an increased content of low- and very low-density lipoprotein cholesterol (LDL and VLDL) in blood plasma.

The surface of lipoprotein particles is negatively charged; accordingly, copolymers with substituted amino groups having a positively charged quaternary nitrogen atom were chosen as plasmasorbents. Various nitrogen atom substituents affecting the electron density shift were used. In that way, it was possible to adjust the magnitude of the positive charge of the sorption center and its hydrophilic-

hydrophobic properties.

There are a number of studies into this subject that have been carried out in recent times; (Bereli *et al.*, 2011; Cao *et al.*, 2011; Dorskaia *et al.*, 2019a; Dorskaia *et al.*, 2019b; Gan *et al.*, 2016; Hou *et al.*, 2013; 2015; Huang *et al.*, 2010; Huang *et al.*, 2011; Huang *et al.*, 2009; Khattari, 2016; Lan *et al.*, 2012; Li *et al.*, 2014; Li *et al.*, 2011; Li *et al.*, 2013; Liu *et al.*, 2016; Liu *et al.*, 2012; Liu *et al.*, 2015; Lu *et al.*, 2013; Lu *et al.*, 2011a; Lu *et al.*, 2011b; Ma *et al.*, 2011; Ma *et al.*, 2008; Teruel *et al.*, 1995; Wang *et al.*, 2016; Wang *et al.*, 2014; Wang & Lan, 2014; Yu, 2013; Yu *et al.*, 2014; Zheng *et al.*, 2011) can be noted. In (Lu *et al.*, 2011a; Lu *et al.*, 2011b) the extraction of lipid profile components by sorbents based on carbon nanotubes modified with various agents was studied. Papers (Hou *et al.*, 2013; 2015; Huang

et al., 2010; Huang *et al.*, 2011; Huang *et al.*, 2009; Lan *et al.*, 2012; Li *et al.*, 2014; Li *et al.*, 2011; Liu *et al.*, 2015; Ma *et al.*, 2011; Ma *et al.*, 2008; Wang *et al.*, 2016; Zheng *et al.*, 2011) are devoted to the binding of LDL with heparin. In (Yu *et al.*, 2014), the authors synthesized the amphiphilic adsorbent based on polyvinyl alcohol (PVA) containing cholesterol ligand and sulfonic dextran ligands. In (Li *et al.*, 2013; Wang *et al.*, 2014; Wang & Lan, 2014) sorbents with ligands of other saccharides are described. In (Lu *et al.*, 2013) authors offered the modified by L-tryptophan carbon sorbent for the extraction of LDL.

Contacting with biological fluids, medical sorbents must be hemocompatible, stable, chemically resistant, standardized, have sorption activity, and not emit toxic substances. However, currently used plasmasorbents often to some degree do not meet these requirements, besides that they can be quite expensive. The developed sorbents are assumed to be cheaper than currently used ones as they are synthesized on the basis of commercially available matrixes. The results obtained are expected to be useful for further investigations aimed at improving the quality and the availability of modern plasmasorption methods.

2. MATERIALS AND METHODS

2.1. Synthesis of the sorbents LP23-30

At the first stage, eight sorbents with groups of trimethylamine, monoethanolamine, and triethanolamine were synthesized. The anion exchanger Lewatit® Monoplus M 500 (see Table 1) was being affected by solutions of amines at heating for 1 h. Water or mixtures of water with isopropanol, propylene glycol, or acetone in a volume ratio of 1:1 were used as solvents. Table 2 presents the synthesis conditions. The choice of the synthesis temperature of 65 °C for the sorbents LP23-25 and LP27-29 was limited by the maximum operating temperature of the Lewatit® Monoplus M 500 (70 °C), and the temperature of 50 °C for LP26 and LP30 – by the acetone boiling point (56 °C). Figure 1 shows the synthesis reactions. Table 1 presents the monomer composition of the copolymers synthesized.

2.2. Determination of the lipoprotein adsorption of the sorbents LP23-30

An in vitro experiment on the sorption of the lipid profile components from plasma was

carried out for the sorbents LP27 and LP29. The samples of sorbents were converted in OH-form and washed by 0.14 N sodium chloride solution. Then the samples were interacting with donor plasma for 3 h. Further, the content of triglycerides (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL) in initial plasma and in plasma after sorption was determined. The analyses were carried out in the Laboratory and Diagnostic Center LDC on the analyzer Architect c8000 (Abbot, USA, manufactured in Japan by Toshiba Medical Systems Corporation) by enzymatic colorimetric methods. The content of LDL and VLDL cholesterol was determined according to Fridvald's (Equations 1 and 2):

$$C_{LDL} = C_{TC} - C_{HDL} - C_{TG} / 2.2 \quad (\text{Eq. 1})$$

$$C_{VLDL} = C_{TG} / 2.2 \quad (\text{Eq. 2})$$

where, C_{LDL} , C_{TC} , C_{HDL} , C_{TG} , C_{VLDL} – concentrations of LDL cholesterol, total cholesterol, HDL cholesterol, triglycerides and VLDL cholesterol correspondingly, mmol·l⁻¹.

3. RESULTS AND DISCUSSION:

3.1. Study of the physico-chemical properties of the LP23-30 sorbents

The following theoretical characteristics were calculated for the initial and synthesized sorbents in chloride and hydroxyl forms:

- total exchange capacity, mmol·g⁻¹ (Equation 3, Figure 2):

$$TEC_f = TEC_0 / (1 + \Delta) \quad (\text{Eq. 3})$$

where, TEC_0 – total exchange capacity of the initial copolymer Lewatit® Monoplus M 500, mmol·g⁻¹; Δ – weight gain per 1 g of the initial copolymer during synthesis, g·g⁻¹.

- crosslinking mass fraction (Equation 4, Figure 3):

$$q_m = 1 - TEC \cdot M \quad (\text{Eq. 4})$$

where, TEC – total exchange capacity, mol·g⁻¹; M – the molar mass of a copolymer unit, g·mol⁻¹.

- crosslinking molar fraction (Equation 5, Figure 4):

$$q_v = q_m / (1 + TEC (M_s - M)) \quad (\text{Eq. 5})$$

where, M_s – the molar mass of the crosslinking agent, $\text{g}\cdot\text{mol}^{-1}$.

Crosslinking molar fraction of the initial and all the synthesized sorbents have the same values since only functional groups replaced during the synthesis, but the ratio of the main-chain units and the crosslinking agent did not change.

For these characteristics, the minimum, the average, and the maximum values were determined, because the ranges of values used for the calculation were given in the Lewatit® Monoplus M 500 product detail sheet. Consequently, also ranges of the calculated values were obtained. For the synthesized sorbents, these parameters were calculated with the assumption that the degree of conversion is 100%. In fact, the degree of conversion is less, and the real values of these indicators are in the range between the values calculated for the initial sorbent Lewatit® Monoplus M 500 (the degree of conversion 0%) and for the full degree of conversion.

The following characteristics, for the studied samples¹:

- bulk density, $\text{g}\cdot\text{ml}^{-1}$ (Equation 6, Figure 5a):

$$\rho = V / m \quad (\text{Eq. 6})$$

where, V – sorbent volume, ml; m – sorbent mass, g.

- specific volume, $\text{ml}\cdot\text{g}^{-1}$ (Equation 7, Figure 5b):

$$V_{sp} = V_{sw} / m \quad (\text{Eq. 7})$$

where, V_{sw} – volume of a sorbent in the swollen state, ml.

As can be seen, the bulk density of the sorbents LP24-26 with groups of triethanolamine is greater than the bulk density

of the sorbents LP28-30 with groups of monoethanolamine. This can probably be explained by the influence of the molar mass of functional groups: in the case of the sorbents LP24-26 functional groups with a greater molar mass than in the case of LP28-30 fall on the same site of the polymer matrix.

The specific volume is the parameter reciprocal of the density of the sorbent in the swollen state. Accordingly, for this parameter, the inverse relationship is observed: for the sorbents LP24-26 with a greater molar mass of functional groups, it is slightly less than for LP28-30.

- coefficient of swelling in water and in various solvents (Equation 8, Figure 6):

$$K_{sw} = V_{sw} / V \quad (\text{Eq. 8})$$

As can be seen, the swelling coefficient of the synthesized sorbents LP23-30 decreases in a row of solvents: water>ethanol>isopropanol. Apparently, this is due to the fact that these sorbents contain both groups of trimethylamine (unreacted groups of the initial copolymer Lewatit® Monoplus M 500) and of triethanolamine (in the case of the sorbents LP23-26) or monoethanolamine (in the case of the sorbents LP23-26). Hydroxyl groups of ethanolamines increase the hydrophilicity of the sorbents, therefore, being more hydrophilic compared to the initial copolymer, the sorbents LP23-30 better swell in a more polar solvent (water) than in a less polar one (isopropanol).

A similar situation is observed for the swelling of sorbents in propylene glycol and acetone. The swelling coefficient decreases in the row: propylene glycol>water>acetone, respectively, reducing the number of hydroxyl groups in this row of solvents (in propylene glycol – 2, in water – 1, in acetone – 0).

As can be seen from figure 6, the difference between the swelling coefficients in ethanol and isopropanol is small, because these solvents are close in structure homologs, differing by only one CH_2 -group. In the case of propylene glycol and acetone, the swelling coefficient differs significantly – by 1.4-1.7 times, which can be explained by a significant difference in the structure of these solvents belonging to different classes of organic compounds.

Further, the sorption exchange capacities

¹ The sorbents were dried to a nominal air-dry state, when the mass decrease was less than 2.1% per week.

on chloride ion of the samples obtained were estimated, and their average values were 2-2.5 mmol·g⁻¹.

3.2. Study of the lipoprotein adsorption by the sorbents LP27 and LP29

The two sorbents – LP27 (with groups of monoethanolamine, solvent – water) and LP29 (with groups of monoethanolamine, solvent – water+propylene glycol) were selected for the experiment on plasmasorption in static conditions. The choice of monoethanolamine groups is due to the fact that earlier studies of a wide range of sorbents of different classes showed good sorption capacity of these groups. The choice of water as a solvent (in the case of LP27) is caused by the fact that it is the most common and available substance, and the mixture of water and propylene glycol (in the case of LP29) – because previous studies showed good results when using the latter.

For these sorbents, the static sorption capacity on the lipid profile components (μmol·g⁻¹) were calculated (Equation 9, Figure 7):

$$S = (C_0 - C_f) V_p / m \quad (\text{Eq. 9})$$

where, C_0 , C_f – initial and final concentrations of a component in plasma, mmol·l⁻¹; V_p – plasma volume, ml; m – sorbent mass per dry weight, g.

As can be seen, the sorbent LP29 has larger capacities on all lipid profile components than the sorbent LP27.

Figure 8 shows the distribution of the sorption capacities of the sorbents LP27 and LP29 by lipoprotein fractions. More than 1/3 of the capacities of both sorbents are spent on the extraction of atherogenic LDL cholesterol, this being a positive factor in terms of the treatment of atherosclerosis. 1/3 of the capacities is spent on HDL cholesterol extraction. Of the two studied sorbents, LP27 has a larger part of the capacity occupied by LDL cholesterol than LP29, and the latter has a larger part of the capacity spent on VLDL cholesterol.

The coefficient of distribution of lipid profile components between the solid and liquid phases (I of plasma : I of sorbent) was determined for the investigated sorbents by Equation 10 (Figure 9).

$$K_d = S / C_f \quad (\text{Eq. 10})$$

As can be seen, the distribution coefficient of all lipid profile components is greater for the sorbent LP29, indicating its good ability to concentrate these substances in its volume.

4. CONCLUSIONS:

The eight sorbents LP23-30 with trimethylamine, monoethanolamine, and triethanolamine groups were synthesized. Their following theoretical characteristics were calculated: exchange capacity (2.63-4.75 mmol·g⁻¹), crosslinking mass, and molar fractions (0.048-0.286 and 0.104-0.375 correspondingly). Physico-chemical properties of the sorbents LP23-30 (bulk density, specific volume at swelling, the swelling coefficient in various solvents) are determined. The experiment on plasmasorption of the lipid profile components for the sorbents LP27 and LP29 in static conditions is carried out. High sorption capacity of these anionites, especially of LP29, was revealed.

The offered sorbents are assumed to be cheaper than currently used ones. The results obtained can be helpful for further investigations aimed at creating modern affine plasmasorbents for cardiovascular diseases treatment.

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Figure 1. Reactions of syntheses of the sorbents LP23-30

Figure 2. Theoretical total exchange capacity of the initial and synthesized sorbents in chloride and hydroxyl forms

Figure 3. Theoretical crosslinking mass fraction of the initial and synthesized sorbents in chloride and hydroxyl forms

Figure 4. Theoretical crosslinking molar fraction of the initial and synthesized sorbents in chloride and hydroxyl forms

Figure 5. Bulk density (a) and specific volume (b) of the initial and synthesized sorbents in a nominal air-dry state

Figure 6. Coefficient of swelling in water and in various solvents of the initial and synthesized sorbents

Figure 7. Static sorption capacity of the sorbents LP27 and LP29 on the lipid profile components

Figure 8. Distribution of the sorption capacities of the sorbents LP27 and LP29 by lipoprotein fractions

Figure 9. The distribution coefficient of the lipid profile components

Table 1. The composition of the copolymers

Copolymer	Monomer units		
	Matrix (initial links)	Matrix (modified links)	Crosslinking agent
Lewatit® Monoplus M 500		-	
LP23-26			
LP27-30			

Table 2. *The conditions of syntheses of the sorbents LP23-30*

Sorbent	Reactant	Solvent	Temperature, °C
LP23	Triethanolamine	Water	65±0,1
LP24		Water+isopropanol	65±0,1
LP25		Water+propylene glycol	65±0,1
LP26		Water+acetone	50±0,1
LP27	Monoethanolamine	Water	65±0,1
LP28		Water+isopropanol	65±0,1
LP29		Water+propylene glycol	65±0,1
LP30		Water+acetone	50±0,1