Outlooks for the Application of Polymers to the Development of New Combined Medical Preparations of Isonicotinic Acid Hydrazide

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Abstract

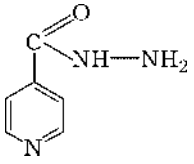
Processes involved in the interaction of some high-molecular compounds with the hydrazide of isonicotinic acid (isoniazid) and (+)-1,1'-ethylenediamine-N,N'-bis-(1-hydroxymethylpropane)dihydrochloride (ethambutol hydrochloride) in aqueous solutions are investigated. The deserving character of viscosimetry to be applied for the investigation of the formation of complexes of polymers with hydrophilic substances is validated for isoniazid and ethambutol hydrochloride. The data obtained are of special interest for the development of the chemistry of medications and for the elaboration of new highly efficient medical products.

INTRODUCTION

At present, the society encounters the problem connected with the necessity to increase life standards and ensure the safety of environments. A solution of this problem is connected with assimilation and rational use of natural resources, removal of pollutants from the environment, development of waste-free and low-waste industry, and an increase in health protection.

One of the directions aimed at a decrease in sickness rate and an increase in the efficiency of prophylactic measures is the development of the chemistry of pharmaceutical substances (PS). Because of this, it is necessary to investigate the processes involved in the interaction of pharmaceutical and auxiliary substances in order to increase the biological availability of preparations, decrease their toxicity and inhibit pharmacological action [1].

In the present work we generalize the results of the investigation of processes involved in the formation of the products of interaction of isonicotinic acid hydrazide (isoniazid)



with (+)-1,1'-ethylenediamine-N,N'-bis-(1-hydroxymethylpropane)dihydrochloride $CH_3-CH_2-CH(CH_2OH)-NH-CH_2-CH_2-NH-CH(CH_2OH)-CH_2-CH_3 \cdot 2HCl$ (ethambutol hydrochloride) with high-molecular substances (HMS) most frequently used in the production of solid remedies [2–5]. These HMS include polyvinyl pyrrolidone (PVP) (molecular mass 300 000), polyvinyl alcohol (PVA) (145 000), water-soluble methylcellulose (MC) (300 000), sodium carboxymethylcellulose (NaCMC) (30 000), soluble starch (37 000), citrus pectine (300 000), complex polymer carrier (CPC) (570 000), β-cyclodextrin (BCD) (1279).

Within the framework of the present investigation, with isoniazid and ethambutol hydrochloride as an example, we demonstrate for the first time the possibility to use viscosimetry to determine the degree of the interaction of a HMS with the hydrophilic low-molecular substances.

The goal of the present work was the investigation of the interaction of isonicotinic acid hydrazide (isoniazid) and (+)-1,1'-ethylenediamine-N,N'-bis-(1-hydroxymethylpropane)-dihydrochloride (ethambutol hydrochloride) with polymers in solution by means of viscosimetry.

EXPERIMENTAL

The polymers used in the investigation were: citrus pectin (Germany), BCD (Hungary), MC, NaCMC (Serbia), starch, CPC, PVA, PVP (Russia). We carried out preliminary viscosimetric determination of the molecular masses of HMS according to the pharmacopeic procedure [6]. The results corresponded to the charts and to the literature data. HMS are used in pharmaceutical industry in the production of solid pharmaceutical dosage forms both in large amounts (as fillers, fluffers) and in small ones (as film-formers and sweeteners), so it is necessary to investigate the mutual effects of PS and polymers in solutions within a broad concentration range. In order to do so, we prepared the solutions with HMS concentrations from 0.02 to 2 g/l, added 10 mg of ethambutol hydrochloride to 50 ml of the polymer solution, and stirred up for 1 h; then the solutions were left for 1 day and again stirred up for 1 h. Investigation of the parameters of polymer solutions was carried out in parallel under the same conditions.

The outflow time of the resulting solutions was measured with the help of Ostvald viscosimeter; relative viscosity (η) was calculated. Determination was carried out according to the general pharmacopeic procedure [6].

RESULTS AND DISCUSSION

In order to estimate the degree of PS–polymer interaction correctly, we calculated the difference of relative viscosity $\Delta\eta$:

$$\Delta\eta = \eta_1 - \eta_2 \quad (1)$$

where η_1, η_2 are relative viscosities of polymer solutions with the addition of a PS and without it, respectively.

The results of calculations are shown in Table 1. It was established by us in the experiment that the relative viscosity of polymer solutions without PS increases in proportion to an increase in polymer content. For instance, it increases for starch from 1.00 to 1.06, for pectin from 1.00 to 1.77, for PVP from 1.00 to 1.03, for PVA from 1.00 to 1.16, for CPC from 1.00 to 1.07, for BCD from 1.001 to 1.002, for MC from 1.03 to 1.82, for NaCMC from 1.00 to 1.46.

We determined that changes in the relative viscosity of HMS solutions in the presence of the substances under investigation are substantially affected by the polymer content. According to the modern theory of polymer solutions, two types of solutions are considered: diluted (with HMS content 0.02–0.2 g/l) and concentrated ones (0.2–2.0 g/l) [11]. Such a choice was due to the features of the behaviour of flexible polymer macromolecules in the solvent (water): a long flexible macromolecule in a diluted solution rolls up and holds inside a definite amount of solvent and therefore the dissolved low-molecular substance. In our investigation, we consider this phenomenon as the behaviour of water and PS. The kinetic flexibility of the polymeric molecular chain increases in the concentrated solutions of HMS, so the nature of the solvent and the substance dissolved in it have a smaller effect on viscosity. Because of this, in order to determine the degree to which an increase in polymer content affects relative viscosity of the solutions under examination, we calculated x value showing the response ratio of an increase or decrease in the relative viscosity of polymer solutions in the presence of isoniazid and ethambutol hydrochloride. Calculation was carried out according to equation

$$x = \Delta\eta_2/\Delta\eta_1 \quad (2)$$

where $\Delta\eta_1$, $\Delta\eta_2$ are differences of the relative viscosity of polymer solutions under investigation with PS additive and without it, for the polymer content of 0.02 and 0.2 g/l in diluted solutions, respectively; 0.2 and 2.0 g/l for concentrated solutions, respectively.

It was determined that the largest effect of PS on relative viscosity of HMS solutions is observed in the case of HMS content (0.02–0.2 g/l). For instance, with isoniazid added, $\Delta\eta$ of solutions of starch, BCD, CPC, pectin, MC, NaCMC increases by a factor of 4.2, 2.4, 95.2, 3.0, 11.9, 44.0, respectively. If the polymer

TABLE 1

Changes in the relative viscosity ($\Delta\eta \cdot 10^4$) of the solutions of ethambutol hydrochloride and isoniazid depending on polymer content of the solutions

Polymer	Polymer content, g/l						
	0.02	0.04	0.1	0.2	0.4	1.0	2.0
			Ethambutol hydrochloride solution				
Starch	4.1	1.1	1.1	11.5	10.6	11.9	0.3
PVP	0.6	0.6	2.0	2.0	6.1	7.1	0.7
PVA	0.9	6.5	279.3	280.0	284.9	285.1	291.3
CPC	312.4	312.6	312.9	313.5	316.8	319.9	323.8
BCD	0.8	0.2	3.2	300.9	306.6	306.9	591.4
Pectin	1.9	3.4	4.1	4.3	878.4	880.4	882.2
MC	11.7	603.6	604.3	604.0	604.7	912.0	932.4
NaCMC	604.2	610.4	612.0	708.9	883.4	889.0	907.0
			Isoniazid solution				
PVP	0	0	9.7	14.0	16.4	18.6	20.2
PVA	0	0	14.8	14.1	13.2	7.4	6.1
Starch	0	0	4.1	17.2	237.5	291.4	325.5
BCD	97.5	129.8	161.0	238.0	441.4	758.7	–
Pectin	294.5	296.3	297.7	886.7	777.2	299.3	181.2
NaCMC	13.6	16.8	324.5	602.9	1534.1	730.7	268.0
MC	220.1	464.8	1205.2	2610.0	1760.6	911.3	831.8
CPC	15.9	319.6	610.4	1513.0	2397.7	3937.0	4896.3

content of solution exceeds 0.2 g/l, a sharp increase in $\Delta\eta$ of solutions is observed only for the case of starch and BCD (by a factor of 18.9 and 3.2, respectively). In MC solutions (0.2–2.0 g/l) with isoniazid added, $\Delta\eta$ decreases by a factor of 3.14.

Ethambutol hydrochloride, which has a different chemical structure (linear) and is a secondary aliphatic amino alcohol, has a different effect on the viscosity of polymer solutions. Similarly to isoniazid, for small HMS content, $\Delta\eta$ of the solutions of PVA, BCD, MC increases by a factor of 311.0, 376.1, 51.6, respectively. However, if polymer content exceeds 0.2 g/l, $\Delta\eta$ increases in the solutions of BCD, pectin, MC, NaCMC by a factor of 2.0, 205.2, 1.5, 1.3, respectively.

The observed phenomena are likely to be explained by the formation of the products of different composition resulting from the interaction between a polymer and a substance, which is connected both with polymer structure and with the properties of monomers comprising a given HMS. It may be assumed on the basis of literature data describing the interaction of different chemical substances with each other that $\Delta\eta$ value is one of the characteristics of the degree of polymer interaction with a substance. A larger $\Delta\eta$ value may mean a more active interaction [7]. So, it may be assumed that pectin, BCD, MC, NaCMC form sufficiently strong products of the interaction with the compounds under investigation; therefore, these polymers can be used as auxiliary substances providing prolonged medicinal action of isoniazid and ethambutol hydrochloride.

The results of our investigation show that the relative viscosity of the solutions of polymers in which glucose and its derivatives are monomers (pectin, BCD, MC, NaCMC) is essentially affected by isoniazid and ethambutol hydrochloride. The effect of these substances under investigation on the relative viscosity of the solutions of polyvinyl pyrrolidone, the monomer of which is vinyl pyrrolidone having a lactam cycle its structure, is insignificant, so it is unreasonable to investigate the interaction

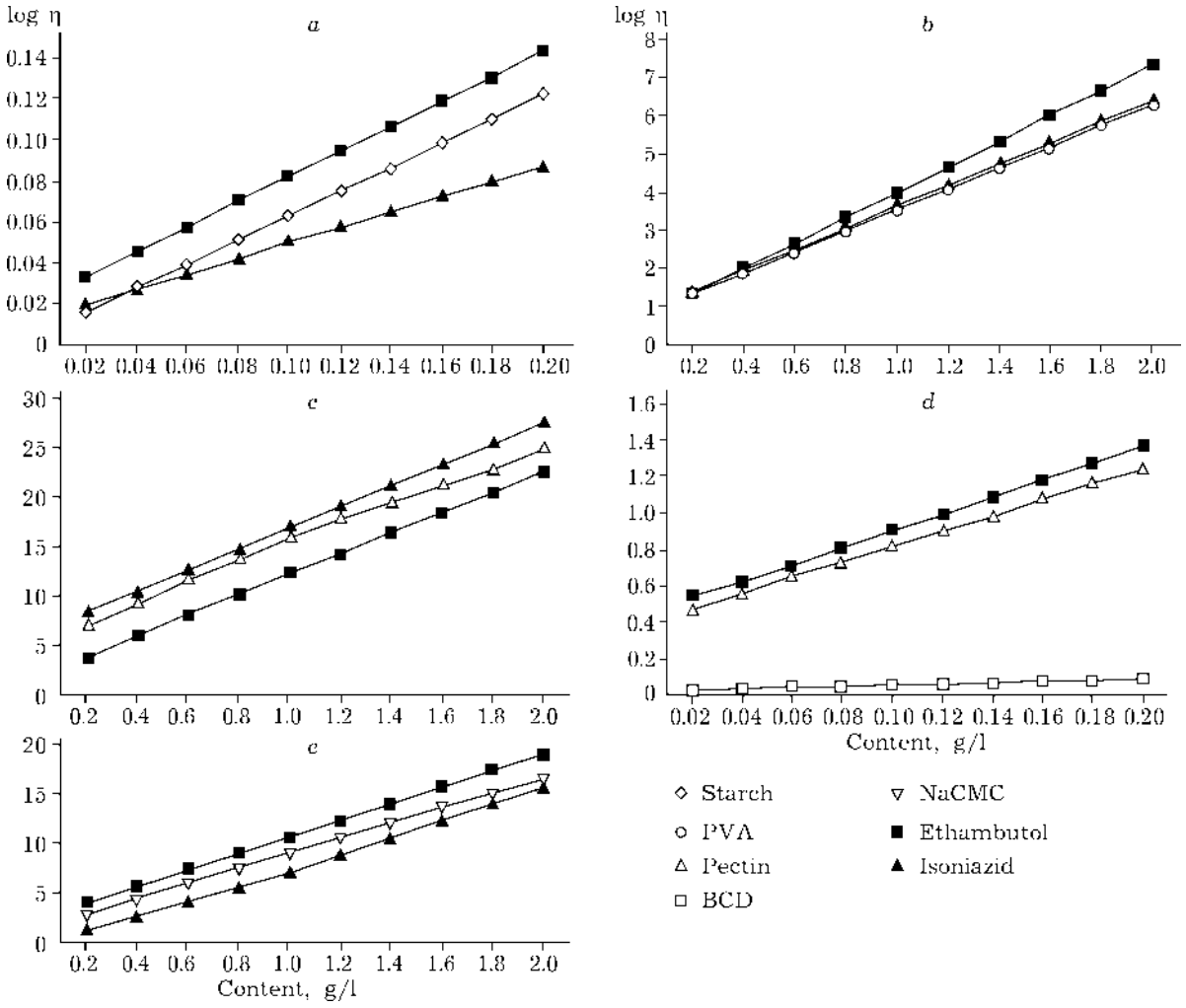


Fig. 1. Dependence of log η on polymer content in solution with isoniazzid and ethambutol hydrochloride added: *a* – starch, *b* – PVA, *c* – pectin, *d* – BCD, *e* – NaCMC.

of this polymer with the substances of interest with the help of viscosimetry.

To confirm the objectivity of results, we calculated log η. The author of [11] described a theory allowing one to estimate the degree of interaction of polymers with various substances; on this basis, we plotted the dependences of log η on polymer content of solutions (Fig. 1).

One can see that a straight-line dependence is observed in all the cases; this may be the evidence of the formation of the products of interaction between a polymer and a substance. It may be assumed that an interaction like the formation of a hydrogen bond occurs in solution. In our opinion, the formation of such a bond will proceed for NaCMC, PVA, and starch, BCD due to the hydroxyl groups present in the polymer structure; in the case of pectin, carboxylic groups also participate in hydrogen bond formation. The substances under investigation differ from each other in their chemical nature. For instance, ethambutol hydrochloride contains two electron-accepting hydroxyl groups with weak nucleophilic properties of the oxygen atom. In turn, isoniazid incorporates an electron-deficient heterocycle (pyridine) and a hydrazine group containing electronegative nitrogen atoms. Therefore, both compounds are able to form a weak hydrogen bond [9, 10]. These assumptions are based on the analysis of literature data showing that polymers may interact with various pharmaceutical substances with the formation of hydrogen or Van der Waals bonds [7, 8].

TABLE 2

Slope ratios of the straight-line dependences of changes in η on polymer content of solutions in the presence of pharmaceutical substances

Polymer	Polymer content, g/l			
	0.02–0.2		0.2–2.0	
	α	tg α	α	tg α
BCD:	3.5	0.061	1	0.017
with isoniazid	28.5	0.543	–	–
with ethambutol	31.5	0.613	23	0.424
PVA:	45	1	35	0.7
with isoniazid	47	1.072	35.5	0.713
with ethambutol	45	1	40	0.839
Starch:	63	1.927	33.5	0.662
with isoniazid	56	1.483	39	0.81
with ethambutol	57.5	1.57	33.5	0.662
Pectin:	–	–	47.5	1.092
with isoniazid	–	–	48	1.111
with ethambutol	–	–	46.5	1.054
CPC:	–	–	11	0.194
with ethambutol	–	–	10	0.176
MC:	–	–	32	0.625
with ethambutol	–	–	35.5	0.713
NaCMC:	–	–	25	0.466
with isoniazid	–	–	25	0.466
with ethambutol	–	–	25	0.466

Note. The dash implied that the dependence is non-linear.

To confirm our assumptions concerning the degree of interaction of polymers in solutions with isoniazid and ethambutol hydrochloride and in agreement with the data of [11], we calculated the angle and slope ratio of the straight line: $\eta_{sp}/c = f(c)$ (η_{sp} is specific viscosity of polymer solutions with PS, c is the polymer content of solution, g/l). Calculations were carried out only for the mixtures for which a straight-line dependence of changes in viscosity on polymer content in solutions with the substances under investigation is observed (Table 2). In the case of non-linear dependence, it is impossible to calculate the angle and slope ratio of the straight line.

The constant k' of the interaction of a polymer with a substance was determined according to equation

$$k' = (\frac{\eta_{sp}}{c} - \eta)/\eta^2 c \qquad (3)$$

Depending on the content and chemical nature of a polymer, k' changes from 0.5 (for pectin solutions) to 2000 (for starch solutions). Calculated k' values for the solutions of pectin, NaCMC, BCD, MC, starch with isoniazid and ethambutol hydrochloride provide evidence of the formation of thermodynamically stable systems; a polymer actively interacts with the substances under investigation in aqueous solutions within the HMS content 0.2–2.0 g/l.

CONCLUSIONS

So, on the basis of the results of investigation, it is proposed to use pectin, NaCMC, BCD, MC as auxiliary substances providing prolonged release of the active substances in the production of solid dosage forms [1, 5, 12–14]. It is necessary to note that starch, NaCMC are optimal fillers, which can be added in any amount with respect to the active substances. Methyl-

cellulose provides an increase in the relative viscosity of the solutions of substances under investigation within the content range 0.02–0.4 g/l, so this HMS can be used within this range as a fluffer promoting mechanical destruction of tablets in a liquid medium. Taking into account the features of the structure of BCD (a cyclic oligosaccharide) and pectin, it is recommended to use them as fillers in the production of granules at a ratio of 1 : 1, which will allow prolonged action of the newly developed pharmaceutical preparations.

The data obtained can be used in solving the questions concerning the optimisation of the composition of auxiliary substances for the purpose of providing the highest completeness and rate of the delivery of a substance into bloodstream [2–4]; these data are of special interest for the development of the chemistry of pharmaceutical substances and for the elaboration of new highly efficient medical products.

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