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Liquid Selective Electrodes for Warfarin Sodium Based on Poly(vinyl chloride) Matrix Membrane

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An accurate, sensitive, selective and reproducible method for quantification of warfarin sodium in pharmaceutical preparation has been developed. This method is based on construction of selective liquid membrane electrodes using phosphotungstic acid as an active material and oleic acid, tri-*n*-butylphosphate, nitrobenzene, acetophenone and di-octyl phthalate as plasticizers and PVC as matrix. The results showed that the linear concentration is between 1×10^{-1} and 1×10^{-5} M, correlation coefficient of (0.9984 and 0.99949), slope of (20.04 -29.6) mV/decade, detection limit of (6×10^{-6} to 4×10^{-5}) M and the life time were (10-40) days. This study also included the measurements of selectivity coefficients of these electrodes in the presence of common cations and some amino acid they found to be less than one. The electrodes were successfully applied for determination of warfarin sodium in pure form and in pharmaceutical tablets.

Keywords: Warfarin sodium, Ion selective electrode, Phosphotungstic acid, Different plasticizers.

INTRODUCTION

Warfarin sodium, 3-(α-acetonyl benzyl)-4-hydroxy coumarin sodium salt is an anticoagulant, used in prevention and treatment of venous thromboembolism [1,2]. Presence of coumarin ring makes warfarin a good complexing ligand. Coumarin complexes are of significant interest because of their biological [3] and complexing ability [4,5]. The chemical formula of warfarin sodium is $C_{19}H_{15}O_4Na$, (m.w.: 330.31 g mol^{-1}) and its structural formula show in Fig. 1.

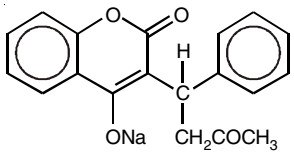

Fig. 1. Structure of warfarin sodium

Crystalline warfarin sodium occurs as a white, odorless, crystalline powder, is discoloured by light and is highly soluble in water, freely soluble in alcohol, slightly soluble in chloroform and in ether [6]. The sodium salt of warfarin has become the most widely used in order to improve the physico-chemical properties of warfarin such as solubility, dissolution rate, hygroscopicity, chemical stability, crystal form and mechanical properties [7]. Warfarin is an anticoagulant drug which competitively depresses the synthesis of vitamin K-dependent coagulation factors [8].

Another factor influencing warfarin bioavailability is its transport in blood, where some 99 % is found bound to the sudlow binding sites of human serum albumin (HSAa) [9]. Currently, the anticoagulant effect of warfarin is indirectly measured through the correlation of the clotting time (prothrombin time) and the amount of the drug present in blood [10].

The most analytical methods have been reported for quantification of warfarin in biological samples are: HPLC with detector of UV-visible [11,12], HPLC with detector of fluorescence [13,14], gas chromatography with detector of mass spectroscopy [15], differential pulse and/or square-wave stripping voltammeters [16,17], fluorescence spectrophotometry [18,19] and capillary zone electrophoresis with detector of PDA [20,21]. In all of these methods the biological sample was prepared. In the present study, several electrodes for the potentiometric determination of warfarin sodium was constructed and characterized. The membranes consisted of an active material with different plasticizers. The electrode parameters were investigated *via* potentiometric measurements including direct, standard addition and titration methods.

EXPERIMENTAL

Warfarin sodium was obtained from (Sammara, Iraq). High molecular weight poly(vinyl chloride) (PVC), oleic acid (OA), tri-*n*-butylphosphate (TBP), nitrobenzene (NB), acetophenone (AP), di-octyl phthalate (DOPH), phosphotungstic

acid (PTA) and tetrahydrofuran (THF) were purchased from Fluka. All metals were also purchased from Fluka. Stock solutions of 0.1 M for each of NaCl, KCl, $CaCl_2$, $MgCl_2$, $Fe(NO_3)_3{\cdot}9H_2O$, $Al(NO_3)_3{\cdot}9H_2O$, alanine, glycine, serine, proline, phenylalanine and arginine were prepared by dissolving (0.292, 0.373, 0.555, 0.476, 2.020, 1.876, 0.445, 0.375, 0.525, 0.575, 0.826 and 0.660 g, respectively with deionized water and making the solution up to 50 mL. More diluted solutions were prepared by subsequent dilution of the stock solutions. A solution of 0.1 M warfarin sodium was prepared by dissolving 1.65 g of standard and making the solution up to 50 mL with deionized water.

Saturated silver electrode (SSE) was used as working electrode and the potential measurements were carried out by using WTW analyzer 740 pH/mV meter (Germany) at room temperature. The ionophore (WFN-PTA) was prepared by starring a 50 mL solution of 0.01 M warfarin sodium and 50 mL of 0.01 M phosphotungstic acid (PTA) at room temperature for 30 min. The ionophore was obtained as white crystals, which was separated and washed with water. The internal solution includes 0.1 M from standard solution of drug to keep injection potential equal zero.

The membranes of various compositions and plasticizers were fabricated by the method available in the literature [22]. The PVC-based membranes have been fabricated by dissolving a mixture of PVC, plasticizer (oleic acid, tri-*n*-butylphosphate, nitrobenzen, acetophenone and di-octyl phthalate), phosphotungstic acid and ionophore in THF (6-7 mL). The components were added in terms of weight percentage. The resulting solution was stirred well and poured in a glass casting ring on a smooth tile. The solvent was allowed to evaporate at room temperature for 48 h in order to obtain the uniform membrane. A membrane sheet about 0.3 mm of thickness and 5 mm diameter was cut away from inner edge and glued it to one end of a glass tube with the help of araldite to avoid leakage.

The potential measurements were carried out with the cell assembly given below:

Outer reference | Test solution | Membrane | internal reference

RESULTS AND DISCUSSION

The study based on membrane carrier have grown exponentially in last decay, because an ion selective electrode (ISE) measure the activity of ion in solution [23]. These properties of ISEs make them good candidature to be used for elemental analysis particularly in medicinal, food and pharmaceutical industries. The present study includes the use of warfarin sodium-phosphotungstic acid as ionophore for the constriction of warfarin selective membrane sensor. The composition of membrane ingredients of ion selective electrode significantly influenced the response characters of electrode. Membranes of various compositions were prepared by using various plasticizers (oleic acid, tri-*n*-butylphosphate, nitrobenzene, acetophenone and di-octyl phthalate), anionic additive (phosphotungstic acid), ionohpore warfarin sodium in PVC as binder material. After several experiments it was found that the membrane with oleic acid as plasticizer has best possible characters. The best composition of the membrane based on oleic acid as plasticizer were investigated (Table-1). The data presented in Table-1 clearly indicates that the membrane with composition of PVC:OA:PTA:ionophore has wide linear concentration range 1.0×10^{-5} to 1.0×10^{-1} M, detection limit (6×10^{-6} M) and fast response time of 20 s.

Plasticizers have a significant effect on the potential response of membrane electrodes. In the present study the effect of various plasticizers *i.e.* oleic acid, tri-*n*-butylphosphate, nitrobenzene, acetophenone and di-octyl phthalate on the potential response of the membrane electrode was investigated (Table-1). It is clearly indicates that oleic acid (electrode I) gives the best results. This could be due to the high polarity of oleic acid as compared to other plasticizers. The detection limit of electrodes assembly was obtained from the intersection of two straight lines portions of calibration curve (Fig. 2).

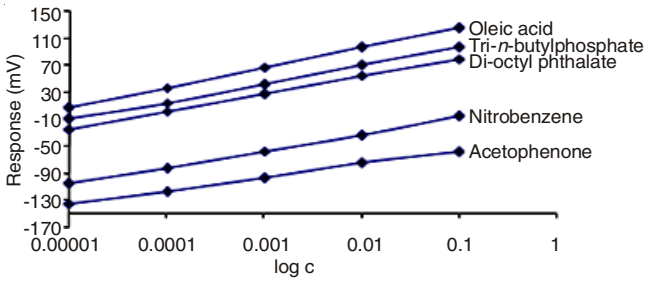

Fig. 2. Calibration curves of WFN-PTA selective sensors

The change in EMF beyond 1.0×10^{-6} M is due to the release of warfarin from inner electrolyte and transported across the membrane. The variation of potential at lower concentration may also be due to the interference of anions due to failure of Donnan exclusion phenomena. It was also observed that the detection limit of membrane sensors using different plasticizers decreases as the dielectric constant of plasticizers decrease. The slops were calculated using the Nernst equation:

$$E_{Cell} = E_{constant} - 2.303\ RT/nF \log a$$

The use of anionic additive phosphotungstic acid in membrane electrode reduces the interference of anions and to decrease

TABLE-1
RESPONSE CHARACTERISTIC OF WFN-PTA SELECTIVE ELECTRODES USING DIFFERENT PLASTICIZERS

Membrane composition	WFN-PTA+OA (I)	WFN-PTA+TBP (II)	WFN-PTA+NB (III)	WFN-PTA+AP (IV)	WFN-PTA+DOPH (V)
Slope (mV/decade)	29.6	27.5	24.7	20.04	26.0
Linearity range (M)	1×10^{-1} to 1×10^{-5}	1×10^{-1} to 1×10^{-4}	1×10^{-1} to 1×10^{-5}	1×10^{-1} to 1×10^{-4}	1×10^{-1} to 1×10^{-5}
Correlation coefficient	0.9994	0.9994	0.9989	0.9984	0.9994
Detection limit (M)	6×10^{-6}	6×10^{-6}	4×10^{-6}	4×10^{-5}	5×10^{-6}
Life time (day)	40	30	15	10	25

WFN = Warfarin; PTA = Phosphotungstic acid; NB = Nitrobenzene; AP = Acetophenone; DOPH = di-octyl phthalate; AP = acetophenone; OA = oleic acid; TBP = tri-*n*-butylphosphate

the electrical resistance of membrane electrode. Phosphotungstic acid itself is an ion exchange, which compete with the ionophore in complexation reaction.

The response time was measured by recording the potential response of electrodes as a function of time when it is immersed in the solution of target ion. The electrodes get the stable potential in a very short time of about 20 s. Thus this time was taken as the optimum response time of membrane electrode.

Since the response mechanism of an ion-selective electrode involves the complexation and decomplexation kinetics between ions and ionophore, therefore no ion selective electrode could be design exclusively to a particular ion, although the ionophore could be more responsive a particular ion over other ions. Thus the selectivity of membrane electrodes (I and II) towards warfarin sodium in presence of other ions was investigated in terms of selectivity coefficient $K^{pot}_{A,B}$ and the data are presented in Tables 2 and 3. The selectivity coefficient was calculated by using separate solution method (SSM).

The potential of the electrode is measured for each of two separate solutions, one containing warfarin sodium (A) of activity a_A and z_A charge (but not B), the other containing the interfering species (B) with charge z_B when ($a_A = a_B$). The selectivity coefficients were calculated using the equation [24].

$$\log K^{pot}_{A,B} = [(E_B - E_A) z_A F/2.303 RT] + (1 - z_A/z_B) \log a_A$$

Tables 2 and 3 showed that the selectivity coefficients for monovalent interfering ions is in the order mono > di > trivalent. This may be attributed to the difference in ionic size, mobility and permeability.

The influence of pH of the test solution on the potential response of electrode assembly was studied at different concentrations (1.0×10^{-2}, 1.0×10^{-3}, 1.0×10^{-4} M) in the pH range of 1-12. The pH was adjusted by adding few drops of 0.1 M NH_4OH and HCl solution. The data presented in Fig. 3 indicates that the potential is constant within the pH range of 3.5-9.5. Therefore this range was taken as the optimum pH range of membrane electrode. However variation in potential below (pH < 3.5) and above (pH > 10) was observed. This is due to the interference of hydrogen ion in the charge transfer process at lower pH and formation of hydroxyl complex of warfarin sodium at higher pH. The effect of pH on the electrode potentials for warfarin sodium selective membrane electrodes was examined by measuring the potentials and the results are listed in Table-4.

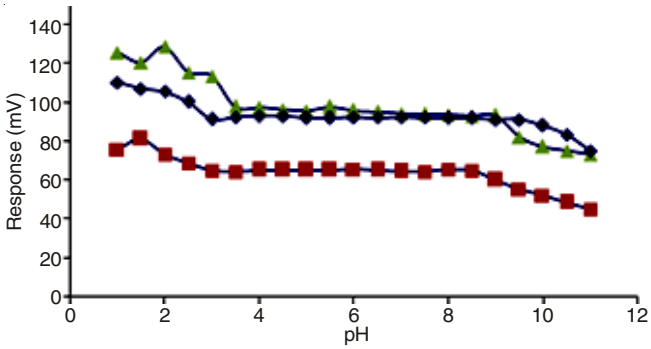

Fig. 3. Effect of pH on potential response of membrane electrode I

TABLE-2
SELECTIVITY COEFFICIENTS AT DIFFERENT CONCENTRATION OF WARFARIN SODIUM USING OLEIC ACID ELECTRODE

Interfering ion	Concentration 10^{-1} M		Concentration 10^{-2} M		Concentration 10^{-3} M		Concentration 10^{-4} M		Concentration 10^{-5} M	
	E_B (mV)	$K_{A,B}$	E_B (mV)	$K_{A,B}$	E_B (mV)	$K_{A,B}$	E_B (mV)	$K_{A,B}$	E_B (mV)	$K_{A,B}$
Na^+	85.1	4.739×10^{-2}	68.2	1.205×10^{-1}	42.7	1.619×10^{-1}	20.1	2.948×10^{-1}	-5.1	4.217×10^{-1}
K^+	100.1	1.522×10^{-1}	82.3	3.609×10^{-1}	54.1	3.932×10^{-1}	22.8	3.638×10^{-1}	-3.4	4.813×10^{-1}
Ca^{2+}	45.3	6.778×10^{-4}	20.4	2.926×10^{-4}	-5.7	1.187×10^{-4}	-12.3	2.371×10^{-4}	-27.6	2.317×10^{-4}
Mg^{2+}	30.7	2.178×10^{-4}	25.6	4.384×10^{-4}	10.7	4.249×10^{-4}	-7.6	3.418×10^{-4}	-15.3	6.031×10^{-4}
Fe^{3+}	-15.2	4.138×10^{-6}	-25.7	3.786×10^{-6}	-31.4	5.071×10^{-6}	-42.6	4.823×10^{-6}	-54.3	4.245×10^{-6}
Al^{3+}	-10.7	5.918×10^{-6}	-15.7	8.177×10^{-6}	-24.3	8.809×10^{-6}	-32.4	1.066×10^{-5}	-40.1	1.281×10^{-5}
Alanine	39.7	1.386×10^{-3}	20.1	2.858×10^{-3}	10.3	1.303×10^{-2}	2.4	7.441×10^{-2}	-12.4	2.39×10^{-1}
Glycine	72.3	1.751×10^{-2}	58.4	5.579×10^{-2}	32.4	7.269×10^{-2}	18.4	2.583×10^{-1}	-5.2	4.184×10^{-1}
Proline	77.3	2.583×10^{-2}	52.1	3.445×10^{-2}	22.4	3.339×10^{-2}	2.2	7.326×10^{-2}	-15.2	1.922×10^{-1}
Serine	-20.4	1.293×10^{-5}	-27.6	6.992×10^{-5}	-37.6	3.138×10^{-4}	-46.7	1.632×10^{-3}	-55.4	8.427×10^{-3}

TABLE-3
SELECTIVITY COEFFICIENTS FOR ELECTRODES AT DIFFERENT CONCENTRATION OF WARFARIN SODIUM USING TRI-*n*-BUTYLPHOSPHATE ELECTRODE

Interfering ion	Concentration 10^{-1} M		Concentration 10^{-2} M		Concentration 10^{-3} M		Concentration 10^{-4} M		Concentration 10^{-5} M	
	E_B (mV)	$K_{A,B}$	E_B (mV)	$K_{A,B}$	E_B (mV)	$K_{A,B}$	E_B (mV)	$K_{A,B}$	E_B (mV)	$K_{A,B}$
Na^+	65.4	8.111×10^{-2}	41.2	9.834×10^{-2}	22.1	2.037×10^{-1}	-5.4	2.160×10^{-1}	5.7	2.142×10^{-1}
K^+	51.4	2.512×10^{-2}	40.1	8.969×10^{-2}	22.4	2.089×10^{-1}	-2.7	2.708×10^{-1}	7.5	2.491×10^{-1}
Ca^{2+}	25.4	9.006×10^{-4}	4.3	4.476×10^{-4}	-10.7	4.134×10^{-4}	-22.4	5.204×10^{-4}	-34.2	7.586×10^{-5}
Mg^{2+}	30.2	1.346×10^{-3}	18.2	1.433×10^{-3}	-5.4	6.443×10^{-4}	-19.3	6.747×10^{-4}	-10.7	1.716×10^{-4}
Fe^{3+}	-45.3	1.647×10^{-6}	-51.4	1.956×10^{-6}	-69.7	9.33×10^{-7}	-80.1	8.916×10^{-7}	-77.5	9.342×10^{-8}
Al^{3+}	-30.1	5.879×10^{-6}	-40.6	4.833×10^{-6}	-55.2	3.142×10^{-6}	-67.9	2.476×10^{-6}	-65.4	2.573×10^{-7}
Alanine	15.4	1.233×10^{-3}	-15.7	8.388×10^{-4}	-30.1	2.576×10^{-3}	-55.2	3.339×10^{-3}	-40.1	4.629×10^{-3}
Glycine	-2.4	2.777×10^{-4}	-12.7	1.078×10^{-3}	-20.7	5.659×10^{-3}	-37.2	1.507×10^{-1}	-35.4	6.861×10^{-3}
Proline	25.4	2.848×10^{-3}	7.2	5.706×10^{-3}	-15.2	8.969×10^{-3}	-25.4	4.117×10^{-2}	-20.1	2.470×10^{-2}
Serine	-70.1	9.589×10^{-7}	-76.2	5.292×10^{-6}	-81.7	3.424×10^{-5}	-89.3	1.921×10^{-4}	-85.4	1.043×10^{-4}

TABLE-4
WORKING pH RANGES FOR WARFARIN SODIUM SELECTIVE ELECTRODES

Number	Membrane composition	pH range		
		1×10^{-2}	1×10^{-3}	1×10^{-4}
I	WFN-PTA+OA	3.5-9.0	3.8-9.5	4.2-9.5
II	WFN-PTA+TBP	5.0-9.5	4.0-9.8	3.5-9.8
III	WFN-PTA+NB	3.8-9.2	4.1-8.9	3.5-9.6
IV	WFN-PTA+AP	4.5-9.8	3.8-9.8	4.3-10.0
V	WFN-PTA+DOPH	3.8-9.0	4.3-9.5	3.5-8.5

WFN = Warfarin; PTA = Phosphotungstic acid; OA = Oleic acid; TBP = tri-*n*-butylphosphate; NB = Nitrobenzene; AP = acetophenone; DOPH = di-octyl phthalate.

Standard analysis: Potentiometric techniques were used for the determination of warfarin sodium these included direct, standard addition (SAM), multiple standard addition (MSA) and titration method. Synthetic solutions of warfarin sodium at concentrations between 10^{-3} and 10^{-4} M were used for the standard addition method using oleic acid and tri-*n*-butyl-phosphate electrodes. The % RC, % RSD and % RE were calculated and are listed in Table-5.

The plot of antilog E/S *versus* the volume of the five additions for 0.1 mL of 1×10^{-1} M standard warfarin sodium solution to the 1×10^{-4} M warfarin sodium is shown in Fig. 4. Table-5 showed that the electrodes based on (oleic acid) and (tri-*n*-butyl-phosphate) as plasticizers were the best electrodes.

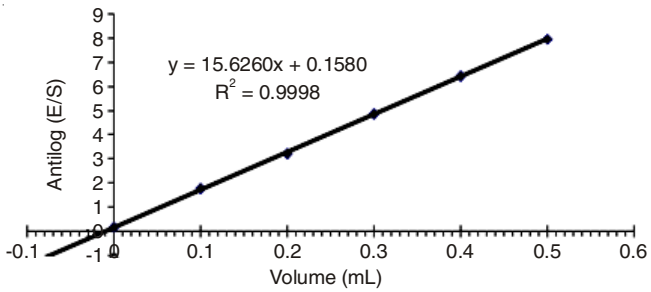

Fig. 4. Plot antilog (E/S) *versus* the value of the added standard for the determination of warfarin sodium solution 10^{-4} M by MSA using (WFN-PTA + OA) electrode

Fig. 5 shows a typical plot for the titration curve of 0.001 M warfarin sodium standard solution with 0.001 M phosphotungstic acid as a titrant using the warfarin sodium electrode based on membrane containing (oleic acid) plasticizer.

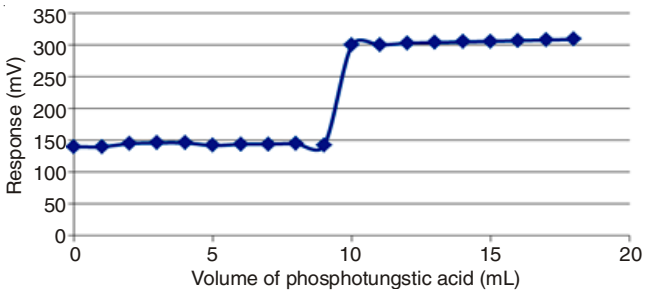

Fig. 5. Titration curve of electrode (WFN-PTA + OA) for drug solution containing 0.001 M warfarin sodium with 0.001 M of phosphotungstic acid as titrant solution at pH 8

The electrodes based on (oleic acid) and (tri-*n*-butyl-phosphate) as plasticizers appearance good parameters therefore applied for pharmaceutical samples. The direct potentiometric method was applied for the determination of warfarin sodium in pharmaceutical tablet (actavis) and (bristol) as listed in Table-6 using the electrode based on membrane (I) and (II). The average recovery for warfarin sodium determination in tablets was around (95.4-106) % with a relative standard deviation of about (0.133-1.6) %, based on an average of 5 measurements for each sample.

Conclusion

Warfarin sodium selective electrodes based on WFN-PTA complex as an active material and with different plasticizers were constructed. The warfarin sodium electrodes based on oleic acid and tri-*n*-butylphosphate were used for drug determination in pharmaceutical preparations. And the electrodes gave excellent parameters and didn't appearance interference with several cations. The proposed analytical method is proved to be simple and rapid, with good accuracy.

TABLE-5
DETERMINATION OF WARFARIN-ION SAMPLES BY POTENTIOMETRIC TECHNIQUES

Electrode No.	Concentration (M)				
	Standard	Measurements using potentiometric methods			
		Direct	SAM	MSA	Titration
WFN-PTA+OA (I)	1×10^{-3}	1.05×10^{-3}	0.994×10^{-3}	0.969×10^{-3}	0.96×10^{-3}
	RSD (%)	0.13*	1.97*	–	–
	RC (%)	105	99.4	96.9	96
	RE (%)	5.0	-0.6	-3.1	-4
	1×10^{-4}	0.986×10^{-4}	0.996×10^{-4}	1.01×10^{-4}	0.95×10^{-4}
	RSD (%)	0.36*	2.4	–	–
	RC (%)	98.6	99.6	101	95
	RE (%)	-1.4	-0.4	1	-5
WFN-PTA+TBP (II)	1×10^{-3}	0.997×10^{-3}	0.985×10^{-3}	0.977×10^{-3}	0.97×10^{-3}
	RSD (%)	0.399*	1.54*	–	–
	RC (%)	102	98.5	97.7	97
	RE (%)	2	-1.5	-2.3	-3
	1×10^{-4}	0.96×10^{-4}	0.971×10^{-4}	0.96×10^{-4}	0.94×10^{-4}
	RSD (%)	0.89*	0.92*	–	–
	RC (%)	96	97.1	96	94
	RE (%)	-4	-2.9	-4	-6

*Each measurement was repeated five times

TABLE-6
WARFARIN SODIUM TABLETS ANALYSES FOR ELECTRODE (WFN-PTA+OA) AND (WFN-PTA+ TBP)

Electrode No.	Parameter	Actavis (tablet)		Bristol (tablet)	
WFN-PTA+OA (I)	Concentration (M)	1×10^{-3}	1×10^{-4}	1×10^{-3}	1×10^{-4}
	Found (M)	1.05×10^{-3}	0.975×10^{-4}	1.06×10^{-3}	1.02×10^{-4}
	RSD (%)	0.09	0.23	0.11	0.15
	RC (%)	105	97.5	106	102
	RE (%)	5	-2.5	6	2
	F-experimental	6.15	11.66	9.22	5.10
	F-theoretical	19.2			
WFN-PTA+TBP (II)	Concentration (M)	1×10^{-3}	1×10^{-4}	1×10^{-3}	1×10^{-4}
	Found (M)	0.975×10^{-3}	0.954×10^{-4}	1.03×10^{-3}	1.03×10^{-4}
	RSD (%)	0.22	0.81	0.13	0.61
	RC (%)	97.5	95.4	103	103
	RE (%)	-2.5	-4.6	3	3
	F-experimental	13.82	18.60	4.99	12.08
	F-theoretical	19.2			

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