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ADVANCED TECHNOLOGIES OF THE TWO-DIMENSIONAL DIFFUSE REFLECTION METHOD IN PHARMACEUTICAL QUALITY CONTROL

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Abstract:

In response to the challenge of viral variability, the development of robust quality control methods for antiviral agents is crucial. This work aims to develop and validate a novel quantitative analytical method for antiviral drug substances based on the kinetics of two-dimensional diffuse light reflection (2D-DLR) with advanced chemometric processing. The approach involves analyzing dynamic speckle patterns using mathematical descriptors analogous to QSAR models, including Wiener (W) and Balaban (J) indices, their Trinaystich modifications (d1, d2, d3), and derived root-mean-square deviations (sd1, sd2, sd3; r1, r2, r3), culminating in a topological descriptor R. The method was applied to model aqueous solutions of Ribavirin (0.25-5 mg/mL, n=6). A family of ten descriptors, visualized as sequential horizontal bands on a 2D diagram, demonstrated high stability for specific samples and effective differentiation between concentrations. The topological descriptor R proved particularly significant, showing a strong correlation (r=0.9998) with concentration. This allowed for the construction of a reliable calibration curve ("R vs. concentration") based on the linear equation y = 170.4 + 55.7·x (r=0.982). Validation according to ICH Q2(R1) guidelines confirmed the method's linearity, accuracy (RSD = 7.19%), and repeatability (repeatability error ε = 7.55%, n=6, P=0.95). In conclusion, the 2D-DLR method combined with tailored chemometric analysis is a reliable and effective tool for the systematic quantification of Ribavirin concentration in aqueous solutions, demonstrating significant potential for the quality control of antiviral drugs.

Keywords: *Antiviral drug quantification; Chemometrics; Diffuse light reflection; Pharmaceutical analysis; Ribavirin.*

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Introduction

In the current context of viral variability driven by their high mutability, comprehensive measures for prevention, control, and treatment with effective antiviral agents are required, along with the development of rapid and reliable methods for quality control. This work is based on an approach employing the kinetics of diffuse light reflection (DLR) from a rough surface, followed by chemometric processing of dynamic speckle patterns. To this end, mathematical descriptors analogous to QSAR models were incorporated into the calculation algorithm: Wiener (W) and Balaban (J) indices in the Trinaystich modification—d1, d2, d3—as well as two triads of root-mean-square deviations sd1, sd2, sd3; r1, r2, r3 (where ri=di/sdi) and $R = \prod_i Ri / \sum_i Ri$.

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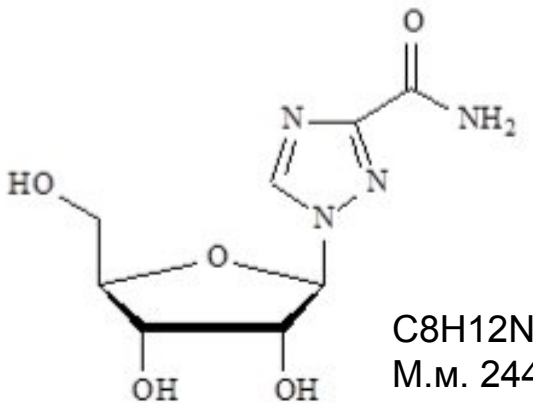
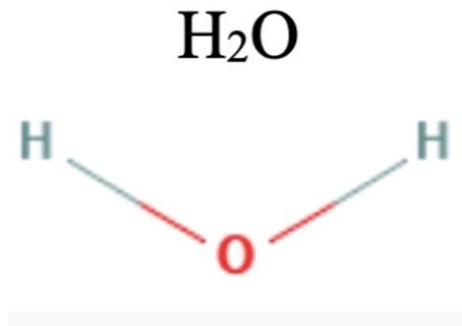
Object of study



C8H12N4O5
M.м. 244,20



- **Ribavirin** is an antiviral drug used for the treatment of severe infection caused by respiratory syncytial virus (RSV), viral hepatitis C, hemorrhagic fever, and other viral infections.
- **Ribavirin** has a structure similar to the purine nucleoside guanine. It disrupts RNA metabolism, which is necessary for viral replication.

- **Bidistilled water** (hydrogen oxide, water) with a conductivity of <5 μS/cm (Bidistillator-BS, NV-Lab, Russia) with a natural content of stable hydrogen-2 nuclei, corresponding to the SMOW-V standard.

Introduction

Research Method

- The study was conducted using the two-dimensional diffuse laser scattering (2D-DLS) method.
- The operating principle is based on the impact of femtosecond laser pulses, generated by an IR emitter with a built-in high spectral density LED, on the smooth surface of the samples

Fig. 1 Schematic of the 2D-DLS equipment: 1 — compact emitter, 2 — laser processing module, 3 — test sample, 4 — collecting lens, 5 — charge-coupled device (CCD), 6 — USB cable, 7 — personal computer.

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C-AREA
d1avgc=0.02505
d1sdc=0.00104
d1left=0.02381
d1right=0.02758
d1top=0.00253
d1bottom=0.00014
d2avgc=7.9380
d2sdc=0.0774
d2left=7.8232
d2right=8.0881
d2top=0.1653
d2bottom=0.0218
d3avgc=0.001271
d3sdc=0.000059

Introduction

Research Procedure

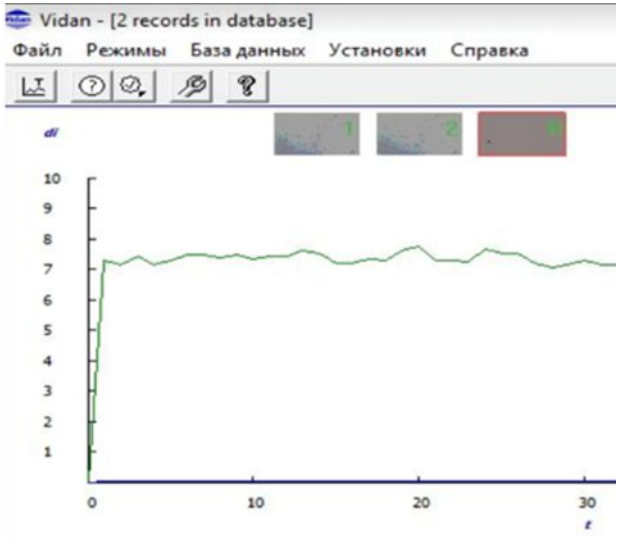
Place the analyzed sample into the cuvette lid up to the level of the manufacturer's mark, maintaining the preset magnification.

↓

Cover it with the cloth and conduct the sample measurement using the VidanCheck software.

↓

Verify the absence of significant spikes (exceeding 2 units).



↓

Enter the average values of the descriptors into the Origin software: d1, sd1, d2, sd2, d3, sd3.

↓

The values of the remaining descriptors (r1, r2, r3, and R) must be calculated using the formulas.

	A(X)	B(Y)	C(Y)	D(Y)	E(Y)	F(Y)	G(Y)	H(Y)	I(Y)	J(Y)	K(Y)
Long Name		d1	sd1	d2	sd2	d3	sd3	r1	r2	r3	R
Units											
Comments								d1/sd1	d2/sd2	d3/sd3	r1*r2*r3/r1+r2+r3
F(x)=								Col(B)/Col(C)	Col(D)/Col(E)	Col(F)/Col(G)	Col(H)*Col(I)*Col(J)/Col(

Results and discussion.

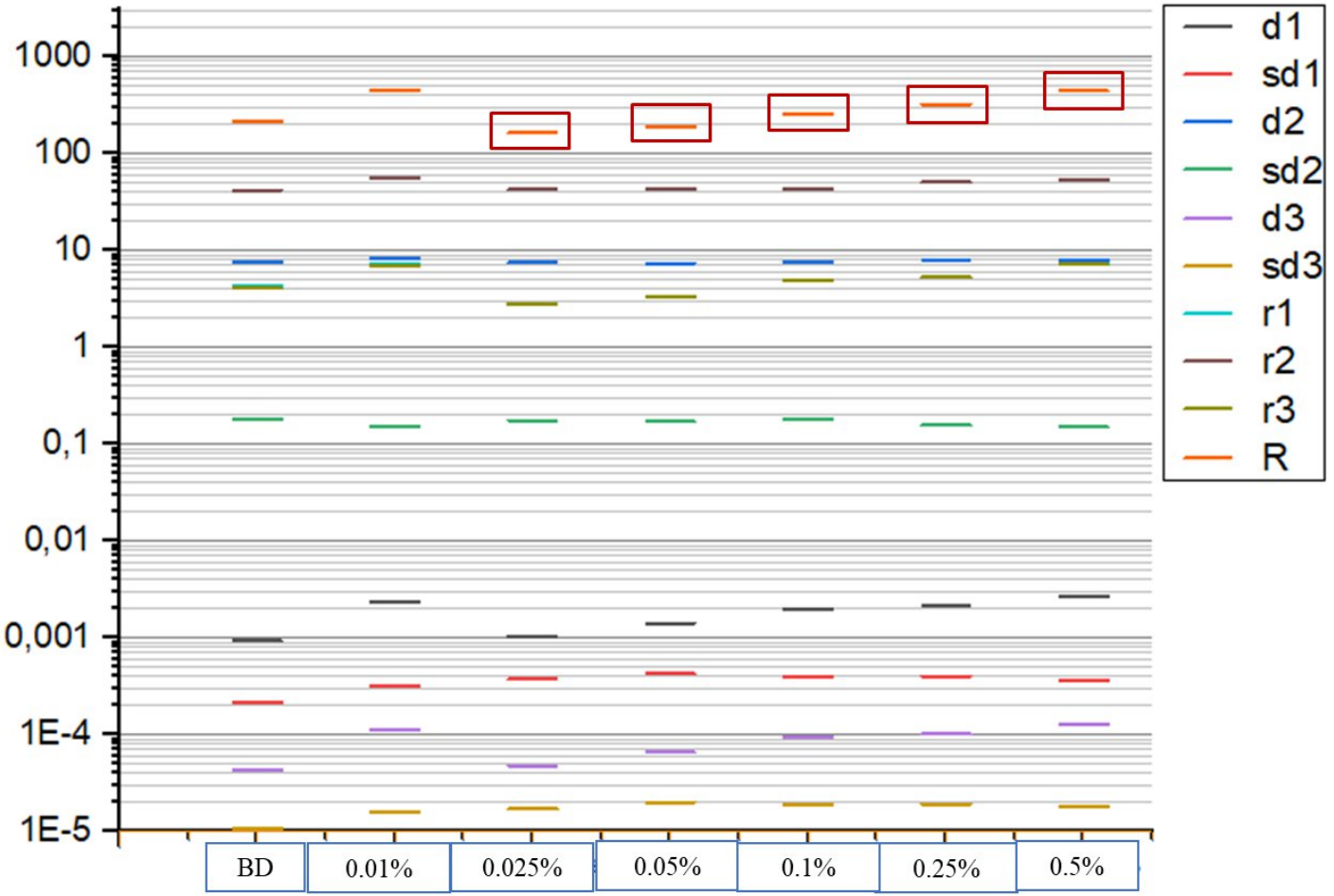


Figure 2. Two-dimensional diagram of the diffuse laser scattering method for aqueous solutions of ribavirin (n=4).

- The values of the descriptors describing the light scattering patterns in the samples can be visually represented as a multidescriptor "fingerprint" diagram.
- A family of 10 descriptors, represented as sequential horizontal bands on the 2D diagram (with didi corresponding to concentration, μg/mL), demonstrated stability of values for a specific sample within intra-laboratory reproducibility, and differentiation among samples with different solution dilutions.

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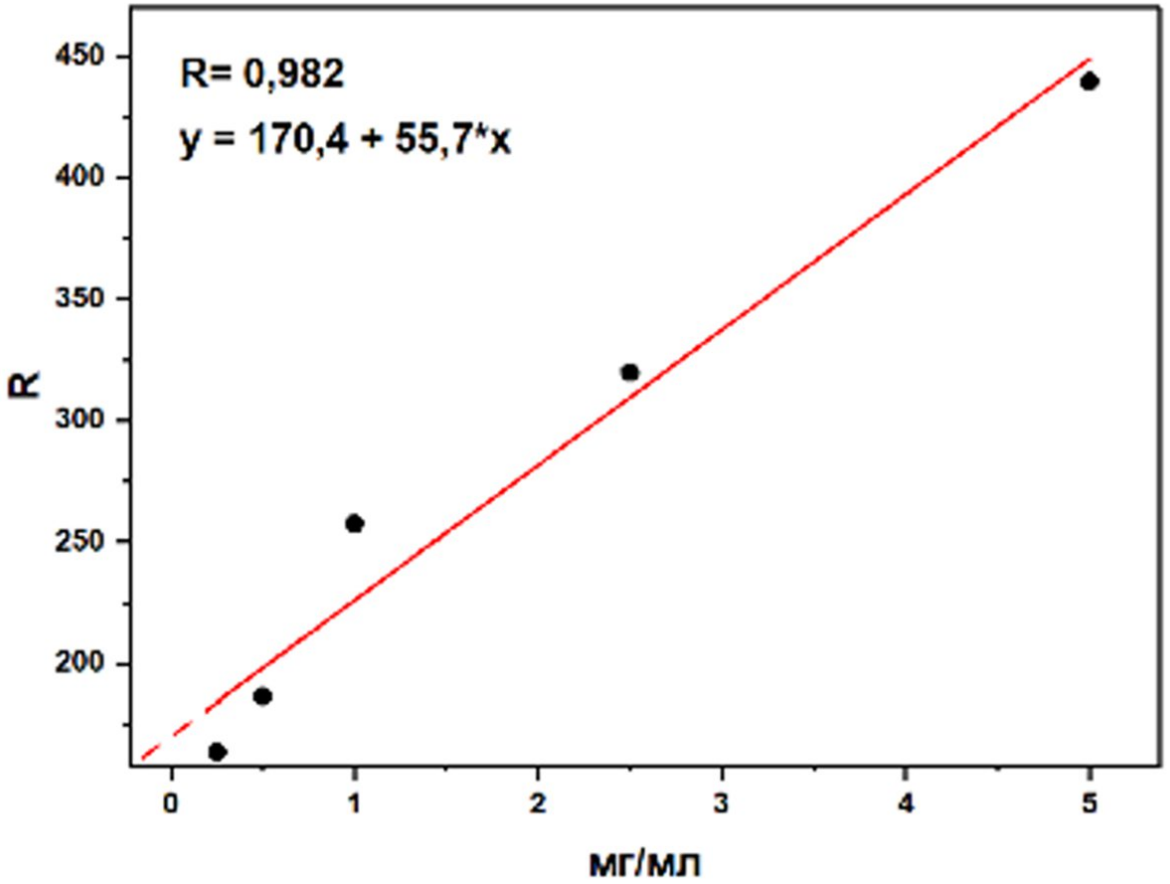
Results and discussion.



To confirm linearity, the following statistical indicators are presented:

- Correlation coefficient (R^2 = 0.982),
- Equation of the line, regression intercept (a = 170.4), slope of the regression line (b = 55.7).
- The resulting calibration line allows for the determination of an unknown concentration of the RBV solution.

- Particularly illustrative and statistically significant was the result for the topological descriptor R.
- This enabled the construction of a calibration curve in the coordinates “R-concentration (μg/mL),” based on the linear equation y=170.4+55.7·xy=170.4+55.7·x, with r=0.982.
- The method was validated according to ICH Q2 (R1) guidelines, confirming linearity, accuracy (RSD = 7.19%), and repeatability (n=6, P=0.95).
- The repeatability error (εε) was determined to be 7.55%, indicating acceptable analytical variability

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Figure 3. Linear (calibration) dependence of "R vs. C, mg/mL" (n=4).

Results and discussion.

Table 1. Repeatability (Intra-method Precision)

C, %	R	$\overline{R}$, c^{-1}	SD	S^2	RSD, %	($\overline{R} \pm \Delta\overline{R}$), c^{-1} $t_{p,f}$ = 2,57 при P=0,95, n=6, f=5
0.1	208,6; 218,9; 214,6; 236,4; 247,2; 208,1	222,3	16,0	255.9	7.2	222,3±16.8

Table 2. Intra-laboratory Precision (Intermediate)

Precision AM (n=18, P=0,95, f=17)						
R, c^{-1}	$\overline{R}$, c^{-1}	SD	S^2	RSD, %	($\overline{R} \pm \Delta\overline{R}$), c^{-1} $t_{p,f}$ = 2,101	$\overline{\varepsilon}$, %
248,6; 259,7; 219,9; 213,2; 274,8; 233,3; 208,6; 310,6; 259,4; 244,4; 247,2; 205,4; 284,5; 214,6; 240,2; 307,6; 247,2; 205,4	245,8	32,8	1075.0	13.3	245.8±16.2	6,6

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Conclusions

The DLR method has proven reliable for systematic quantitative determination of concentration, which may be used in future standardization and quality control of ribavirin.