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Research Article

Express method for particle size analysis in solid, liquid, and amorphous materials using 3D calibration curve and 2D-DLS dynamic light scattering

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Abstract

This study proposes a new method for particle size studying based on the use of topological descriptors for various media and types of matter. The sizes of supramolecular particles in water-lactose complexes were studied using the diffuse dynamic light scattering (DLS) method. Mist-Standart latex balls were used to generate a 3D calibration curve, followed by empirical particle size determination. In order to confirm the output, the resulting sizes were compared for a number of silver proteinate solutions, preliminary analyzed by laser light scattering (using ZetaSizer equipment by Malvern Instruments Ltd, UK). The new method uses a simplified procedure, provides a quick solution and may be used for both quality control of cloudy and opaque medicinal substances and excipients as well as in other fields of nanotechnology.

Keywords: nanoparticles, particle size, silver proteinate, latex nanoparticles, dynamic light scattering

INTRODUCTION

There are a large number of instrumental methods for determining the size of nanoparticles in solutions [1, 2]. Laser-based analytical methods [3], such as static and dynamic laser light scattering [4, 5], are widely used, both separately and in combinations with other physical and chemical techniques. These methods, however, are subject to a number of restrictions [6]. More specifically, the researcher has to establish the exact characteristics of particles in the test sample [7], which is very time-consuming. There are also restrictions on the medium holding the sample. It should be noted that the light-scattering pattern processing method [8] was used for analyzing the data collected by the detector of the device. The direct particle size in this case was established by solving an inverse ill-posed mathematical problem with an uncertain solution.

The experimental work completed to study the kinetics of physical and chemical properties of the lactose preparations duly registered as medicinal products (reg. No. (ЛП-N (000035)-(РГ-RU)) in the State Register of Medicinal Products has confirmed that certain particles formed in the product solutions may be classified as nanosized particles [9]. In addition to the direct detection of supramolecular water-lactose complexes, it is most important to establish the size of such complexes and subsequently rate them as nanoparticles, since this criterion plays one of the central roles for the biological activity of a medicinal product.

This study proposes a new, more rapid method for various media based on the analysis of light scattering in density inhomogeneities (diffuse light reflection method) with the light scattering pattern processed using topological index equations [10]. The use of latex nanoparticles of a known size allowed plotting a calibration model that was then applied to establish the size of the supramolecular water-lactose complex by the two-dimensional dynamic light scattering method (2D-DLS) [11]. The work was aimed at accelerating quality control in the development and production of nanosized medicinal products, as well as at eliminating all currently existing restrictions on the media holding the active substance particles.

MATERIALS AND METHODS

In the study, 5% solutions were prepared for the lactose preparations duly registered as medicinal products (reg. No. (ЛП-N (000035)-(РГ-RU)) in the State Register of Medicinal Products. For the purpose of measurements by the 2D-DLS method, the solution was prepared at the rate of 0.75 g of preparation per 15 ml of buffer solution. An accurately weighed sample of 0.7500 g was added into the weighing bottles. Then, 15 ml of buffer solution was added into a 50 ml beaker. A magnetic stirrer was placed in the beaker. The weighed sample was then added in the beaker while stirring (moderate rate, no vortex formation). After adding the weighed sample, the solution was left to mix for 5

to 7 minutes. The resulting solution was poured into a Petri dish. All groups to be compared were measured using each of the devices strictly on the same day to ensure a valid subsequent comparison of the results.

The 2D-DLS method uses a technical solution to register the diffuse reflection, enabling a study of the neutron-induced microoscillations of the supramolecular complexes on the sample surface. The resulting light scattering patterns were processed using ten topological descriptors similar to those of Wiener and Balaban–Trinaistich [12] applied in QSAR models (Syroeshkin A.V. et al., 2009). Each descriptor is a topological convolution of the light scattering matrix obtained through element-by-element elimination of the background [13]. For data processing, the Vidan® and Atrium software was used, developed by our team at the Department of Pharmaceutical and Toxicological Chemistry of the Peoples' Friendship University of Russia.

The dynamic laser light scattering method [14] was used to assess reliability of the results obtained and establish the exact size of the particles selected as verification models. This method is used to analyze the size and size distribution of molecules and particles, most commonly, in the submicron/nano range, that are dispersed or dissolved in a liquid [15]. The Brownian motion of particles or molecules leads to rapid fluctuations of scattered light intensity [16]. An analysis of such short-term intensity fluctuations allows establishing the velocity of the Brownian motion and, as a consequence, the particle size in the sample to be analyzed (using the Stokes–Einstein equation). All measurements were performed using a ZetaSizer series laser-based hydrodynamic particle size analyzer (by Malvern Instruments Ltd, UK). The refraction index was preliminarily determined for each solution by refractometry.

RESULTS AND DISCUSSION

The total array of descriptors used in the calculations is shown in Table 1. The 3D calibration model was made using descriptors R1 and d3 and measurement results for a large set of Mist-Standart latex balls with predetermined sizes and ideal spherical shapes.

Table 1: Descriptor Calculation Table for 20–1000 nm Latex Particles.

	d1	sd1	d2	sd2	d3	sd3	R1	R2	R3	R	Size (nm)
1	0,3035	0,0728	8,3424	0,3037	**0,0160**	0,0042	**4,1691**	27,4692	3,8008	0,0814	**20**
2	0,8162	0,2958	9,7749	1,0937	**0,0557**	0,0242	**2,7589**	8,9375	2,2996	0,2468	**40**
3	0,1074	0,0656	8,4185	1,5225	**0,0069**	0,0054	**1,6374**	5,5294	1,2830	0,7274	**60**
4	0,0784	0,0099	8,9858	0,2934	**0,0052**	0,0007	**7,9584**	30,6265	7,1324	0,0263	**80**
5	0,0369	0,0168	8,2442	0,4867	**0,0021**	0,0010	**2,1925**	16,9390	2,1028	0,2719	**100**
6	0,0383	0,0363	8,3715	0,6867	**0,0023**	0,0023	**1,0559**	12,1909	1,0070	1,0996	**200**
7	0,0215	0,0112	8,3779	0,4788	**0,0012**	0,0007	**1,9146**	17,4977	1,7396	0,3630	**300**
8	0,0539	0,0513	8,2008	0,9986	**0,0034**	0,0035	**1,0505**	8,2123	0,9724	1,2201	**400**
9	0,0263	0,0090	8,4522	0,3325	**0,0015**	0,0006	**2,9124**	25,4202	2,5312	0,1647	**500**
10	0,0561	0,0287	8,2924	0,5432	**0,0032**	0,0019	**1,9502**	15,2658	1,7370	0,3665	**600**
11	0,0327	0,0096	8,9208	0,4910	**0,0020**	0,0007	**3,3967**	18,1686	3,0031	0,1326	**700**
12	0,0159	0,0109	8,3511	0,5354	**0,0009**	0,0007	**1,4588**	15,5979	1,3584	0,5958	**800**
13	0,0978	0,0260	9,7358	0,6201	**0,0069**	0,0023	**3,7569**	15,7004	3,0444	0,1253	**1000**

The significance of differences between the groups was assessed using statistical analysis: the device was used to process the results obtained after three measurement cycles. Origin Pro software was applied to plot curves and process the results statistically.

The particle sizes of reference substances (silver proteinate solutions) were preliminarily estimated (fig. 1) using a Zetasizer Nano ZS unit (by Malvern Instruments Ltd, UK). The resulting size spectra provide information on the average size of the most voluminous fraction of particles (as a percentage of the total volume).

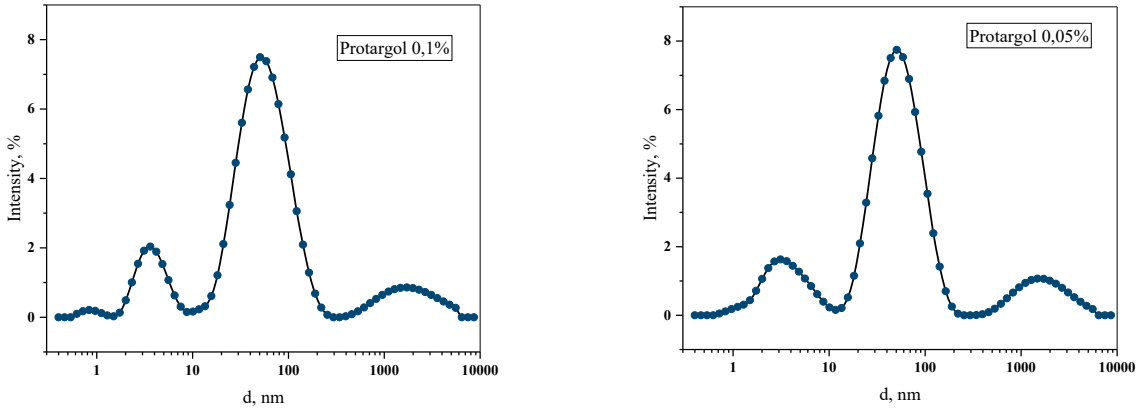

Figure 1: Protargol Sample Particle Size Distribution (0.2% and 0.05%).

The calibration curve example shown in Figure 2 was obtained using the pair of descriptors that enabled the most convenient interpretation of the measurement results in order to establish the sizes of supramolecular particles. All points indicated on the calibration curve were found corresponding to the particle sizes of the size spectra.

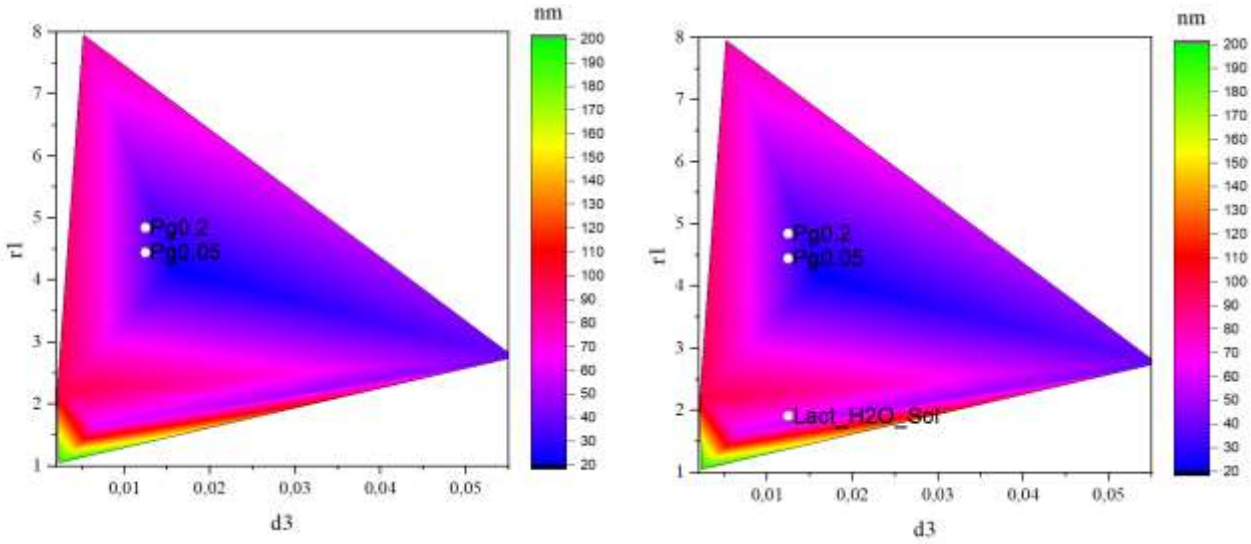

Figure 2: Calibration 3D Model for Determination of Particle Size in the 20–200 nm Range.

The values obtained were then plotted on the calibration curve in order to empirically establish the particle sizes for the water-lactose complexes. It may, therefore, be establish that the size of the water-lactose complexes in the medicinal product sample (Reg. No. ЛП-N (000035)-(РГ-RU)) is approx. 50–70 nm and the preparation may be rated as a nanosized product.

It should be noted that when implementing this method for estimating the sizes of supramolecular complexes in a sample, a photon wave perturbation, which is caused by the impact of a thermal neutron, rather than the nanoparticle is used as the light-scattering object. The dependence of the descriptor on the particle size in the sample, when analyzed by mathematical correlation, was not linear, while the oscillations were monotonous. For the n-dimensional space presented, applicability of the diffuse light reflection method has been confirmed, with its advantages including the ability to compare groups of samples under study based on the ratio of several mathematical descriptors describing these groups (the Atrium software was used). The method described shows great promise, since the pharmaceutical industry currently uses a wide range of medicinal products in forms other than colorless or colored clear solutions, which cannot be analyzed by the laser-based methods. The technique described in our work enables studying and quality control for preparations with nanoparticles immersed in cloudy and opaque media, as well as for preparations in the amorphous, solid, or powder forms. In addition to its rapidity, zero sample preparation requirements, and the possibility of conducting analysis without destroying the sample with concentrated acids or heating, the method proposed has another definitive advantage: it may be used to control the quality of pharmaceutical substances without even opening the package. This is feasible when the medicinal product package is made of a transparent plastic or glass material. This study has a wide range of practical applications.

CONCLUSIONS

The results obtained indicate that the method described allows for quick determination of the size of nanopreparations immersed in cloudy opaque media and presented in the forms of ointments, gels, solid amorphous or powder substances, without destroying the sample. The method proposed was used to successfully establish the particle size of a preparation (50–70 nm) registered as a medicinal product (Reg. No. (ЛП-N (000035)-(РГ-RU)) in the State Register of Medicinal Products,

and its efficiency was verified by comparing the particle sizes in silver proteinate solutions with the results obtained by laser light scattering. It may, therefore, be concluded that an active pair of descriptors shall be preliminarily selected for each new sample analyzed that would allow establishing the particle size most accurately and adequately by the above method. The results obtained are of great practical importance in terms of their potential application in quality control of pharmaceutical substances and medicinal products.

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