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Laser diffraction for standardization of heterogeneous pharmaceutical preparations

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Abstract

A new quantitative method for standardization of heterogeneous pharmaceutical preparations and their quality control during storage based on laser diffraction is proposed. A series of pharmaceutical dosage forms - suspensions, emulsions, tinctures, decoctions, cell preparations and others, are heterogeneous medicines. In some cases disperse phase can be formed during storage as a result of layering (L_1/L_2) or precipitation (S/L).

Laser diffraction method proposed in this study can be used for standardization and quality control of medicines.

Keywords: Laser diffraction; Heterogeneous pharmaceutical forms

1. Introduction

Particle size distribution in heterogeneous systems is studied in various fields of science from colloidal chemistry and oceanography to cytology and pharmaceutical chemistry [1–6].

On the pharmaceutical market heterogeneous medicines are widely presented. Most frequently prescribed pharmaceutical dosage forms are powders, microcapsules, suspensions, emulsions, aerosols, mixtures, tinctures. Decrease in aggregation stability of heterogeneous as well as homogeneous medicines results in emulsions stratification and suspensions sedimentation, which negatively influences efficacy and safety of medicines.

Morphology change of cells at various pathologies can be used for diagnostics and monitoring of treatment. For example, based on the size distribution of infectious pathogens the monitoring of children leucosis remission is possible [2].

The cell distribution (in affected tissues) by size and form may serve as a basis in diagnosis of diseases of different ethiology as well as in control of efficiency of a treatment. The method can be applied in early diagnosis and efficiency control in therapy of infectious diseases of the upper respiratory organs, diseases of the central nervous system of unknown etiology (multiple sclerosis), urological and gynecological diseases.

2. Experimental

2.1. Equipment

Particles distribution by the size and the form was registered with laser diffraction particles sizes identifier (particle sizer) “Malvem 3600 Ec” [7]. The helium-neon laser emit a monochromatic beam of light ($\lambda_{max} = 633$ nm) which passes through an experimental cell. In an experimental sample all particles pass through the illuminated zone due to continuous mixture using the built in ultrasonic and magnetic mixers. Diffraction pattern was focused on the multielement photodiode detector by using Fourier lenses. The detector was directly connected to a computer which served for a data processing involving integration of a set of diffraction patterns reflecting instant particles distribution by size. For the analysis of the particle size distribution and the shape of cells two kinds of dependences were used: $n_i = f(r_i)$ and $v_i = f(r_i)$, where n_i and v_i are the number and volume fractions of dimensional group r_i, respectively. Sensitivity of a technique

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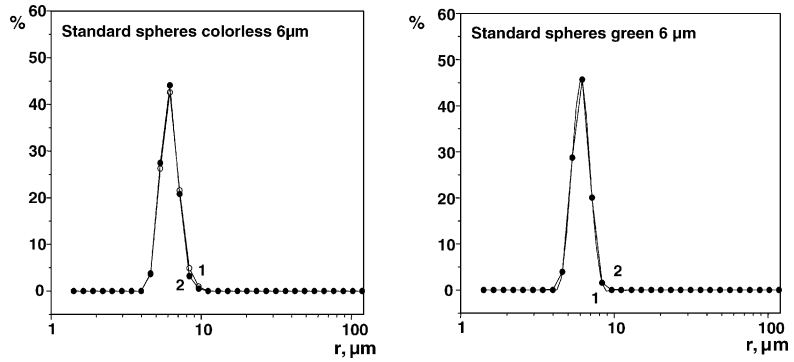

Fig. 1. Volume (–◯–) (1) and number (–●–) (2) distributions of standard 6 μm spheres.

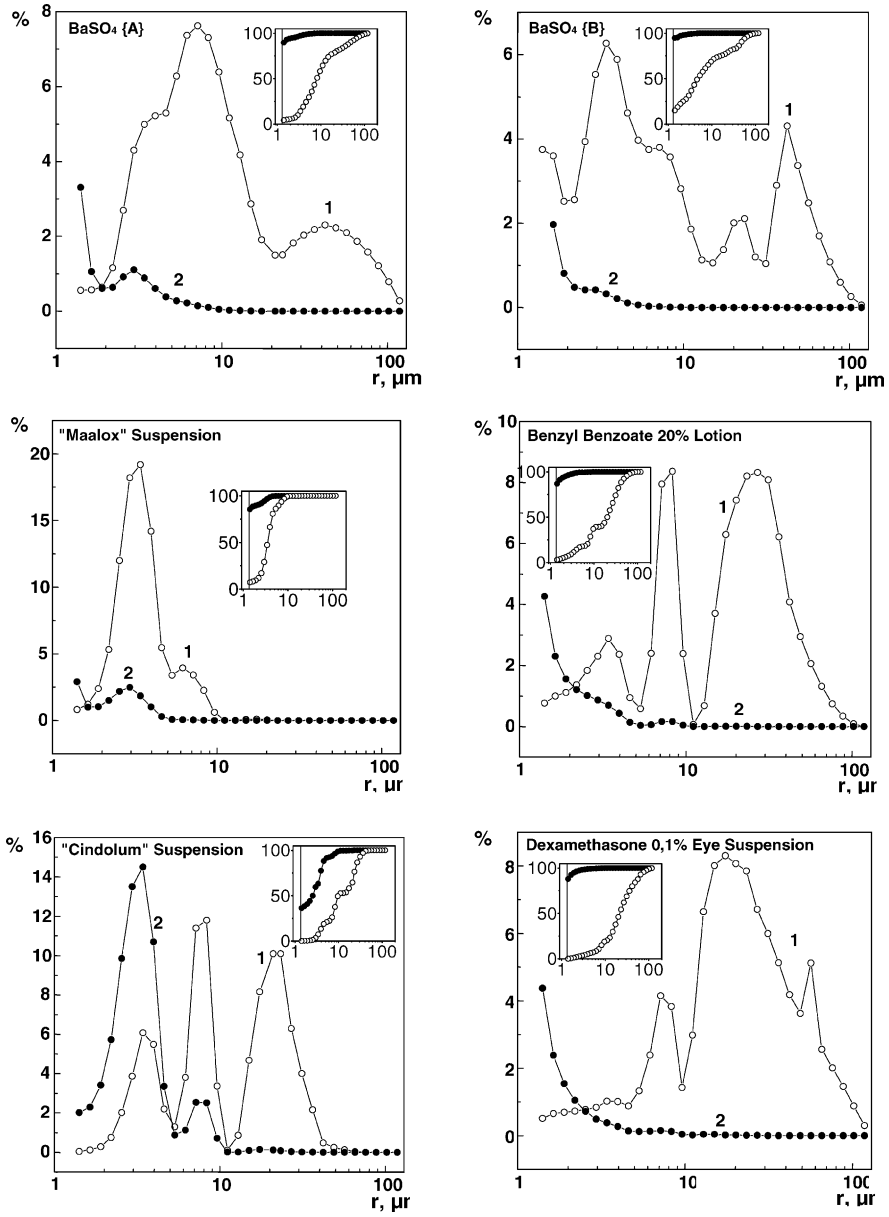

Fig. 2. Volume (–◯–) (1) and number (–●–) (2) distributions of particles of suspended pharmaceutical dosage forms and radio-opaque $BaSO_4$-based by various manufacturers (A, B), integral curves in insertions.

Table 1
Change of the integrated characteristic of tinctures dispersion during storage, $T = 23\,^{\circ}C$, average ± mean-square deviation ($N = 9$), $P = 0.95$

Tincture	The specific surface area (m^2/sm^3)	
	At the moment of purchase	After 60 days storages
Hawthorn	0.0951 ± 0.0021	0.0937 ± 0.0040
Motherwort	0.2477 ± 0.0676	0.1034 ± 0.0076
Valerian	0.2670 ± 0.0185	0.1062 ± 0.0084

depends on the sectional area of particles and vary in an interval from 500 particles in sample (at length ~0.5 mm and average width ~70 μm) up to ~10^4 particles in sample (at the average linear sizes about 1 μm) that provides a possibility to investigate practically any heterogeneous system. The measurement requires 3 (10) ml of sample and can be performed in 3 min. Before measurement samples undergo dilution with water.

Measurement of standard 6 μm spheres for validation of laser diffraction method has been carried out (Fig. 1). Figures show the experimental results and accuracy of measurement in terms of particle size, number and volume distributions.

2.2. Pharmaceutical dosage forms

Suspensions of “Cindolum”, “Maalox”, “Dexamethasone”, radio-opaque $BaSO_4$-based medicines, “Benzyl

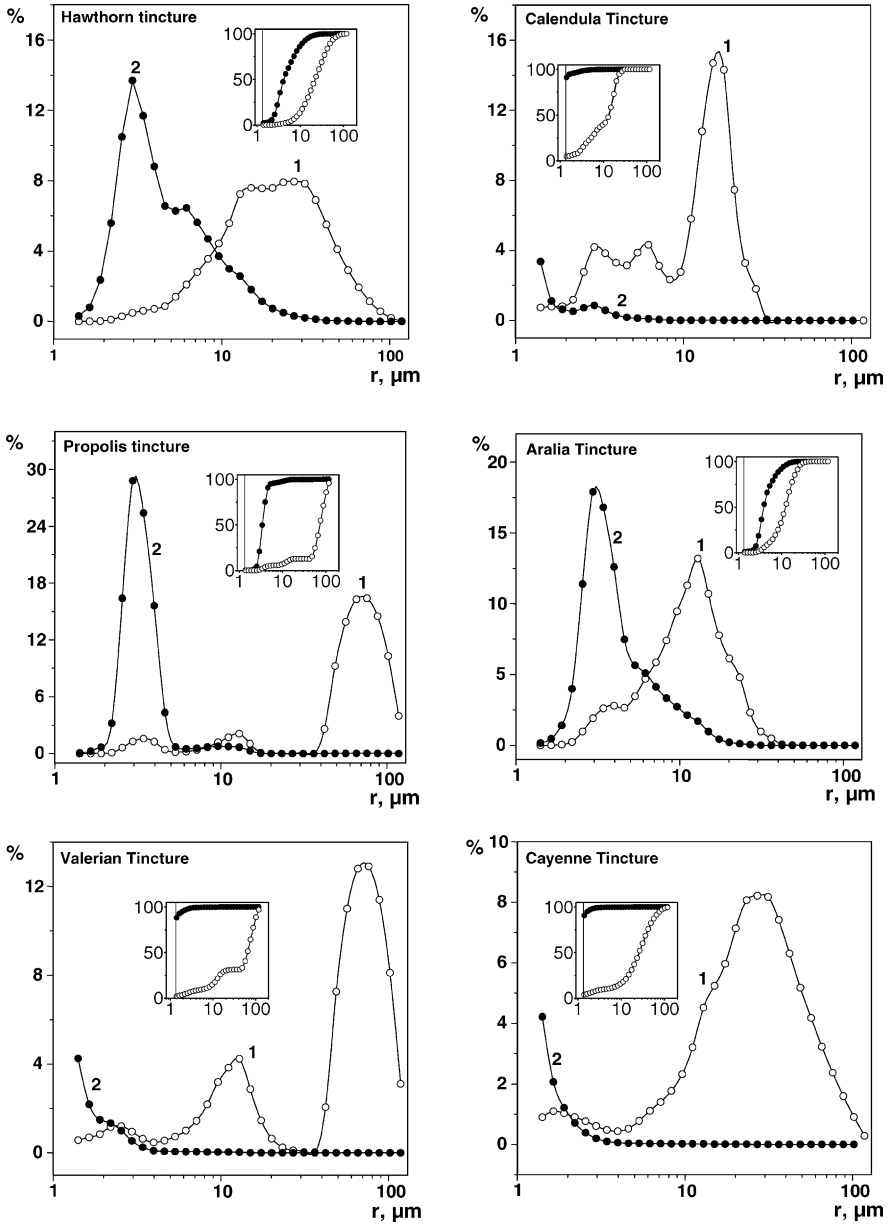

Fig. 3. Volume (–◯–) (1) and number (–●–) (2) distributions of disperse phase particles in tinctures, integral curves in insertions.

Benzoate Lotion", as well as the tinctures of Calendula, Motherwort, Valerian, Hawthorn, Peony, Pepper siliculose, Sulfacyl Sodium Eye Drops have been analyzed.

3. Results and discussion

The major advantage of the method used in this study for the description of heterogeneous systems is a possibility to find out a correlation between the properties of heterogeneous system and particle size (and shape) distribution. Existence of such dependence is determined by features of the method. Statistical morphometric estimation is carried out for the whole sample, i.e., taking into account all particles, instead of sampling of 10–100 particles of disperse phase as it occurs in microscopic method. Moreover, collecting the information about both, number and volume of the particles allows to reveal fractions with a small number of large particles.

Dispersion of radio-opaque barium sulfate-based medicines from different manufacturers (Russia, Germany) (Fig. 2) was analyzed by the method of laser diffraction. It has been found that particles less than 1.4 μm prevailed in all medicines. According to radiological experiments the greatest radio-opaque effect is observed at $r = 1–3$ μm. Therefore, $BaSO_4$ {A} is preferable for radiological practice, than $BaSO_4$ {B}.

Variation of particle size distribution of the heterogeneous medicines under various storage conditions (Table 1) indicates that the ageing of a preparation causes the change of its pharmacological properties. Twenty percent Benzyl Benzoate Lotion is a good example showing how important is for a heterogeneous medicine to meet a required dispersion. This drug is used for treatment of scabies [4,5]. During emulsion storage the sedimentation of particles of the disperse phase was observed together with decrease in substance activity. Thus, efficiency of treatment reduces. At the same time the adverse effects appear: a contact dermatitis appeared in a place where the lotion was applied.

Extremely important problem solved applying the described method is the control of a disperse phase formation in homogeneous medicines, for example in tinctures. In all analyzed homogeneous drugs, for example in tinctures with valid period of storage, there were particles of a disperse phase with a size from 1 μm up to 100 μm (Fig. 3). Thus, we observed the certain "portrait" distinctions in the tinctures obtained from different medicinal herbs.

It is possible a priori to state, that occlusion or adsorption of active compounds on disperse phase particles of tinctures will affect their bioavailability and absorption kinetics. Various storage conditions of tinctures of Valerian; Hawthorn and Motherwort effected not only agglomeration of the particles, but also by reduced the polydispersity (Table 1).

It was revealed that change of Hawthorn and Valerian tinctures particle size distribution spectra are more informative in respect to the quantitative characteristic of ageing, than absorption in ultraviolet and visible spectrum, those only slightly change during storage.

It has been also found that some of investigated medicines prepared by dissolution of individual substances also contain particles in an interval from 1 μm up to 100 μm, for example 20% Sulfacyl Sodium Eye Drops.

4. Conclusions

Simplicity of experiment, short analysis time and reach and reliable information provided by small angle laser diffraction makes this method very useful for standardization and quality control in pharmaceutical industry as well as for technology optimization. After creation of particle size distribution libraries of various manufacturers, the method will provide an opportunity of authenticity control of drugs.

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