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Organic nanoparticles

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Abstract. Physical and chemical methods for the synthesis of nanoparticles of complex organic compounds (mechanical grinding, laser ablation, solvent replacement, reduction in solution, ion association, *etc*.) are analyzed. Emphasis is placed on a method that employs supercritical fluids and on cryochemical synthesis. Physicochemical properties of nanoparticles of organic compounds and the prospects of their use are considered. The bibliography includes 130 references.

I. Introduction

Nanoscience is a multifunctional discipline that embraces such wide areas as nanotechnology and nanochemistry. Nanotechnologies are aimed at the preparation of nanoparticles with novel properties and the development of materials and devices on their basis. This is one of the topical directions of natural science in the 21st century.

The development of nanochemistry is associated with transition from the microscale level to nanosizes. Studying nanosized particles resulted in the discovery of size effects, which can be considered as a new degree of freedom imparting new qualities to chemical compounds and resulting in earlier unknown chemical transformations.

The investigations evolved in such a way that the first efforts were directed at the studies of atoms, clusters, nanoparticles of different metals, semiconductors, fullerenes, carbon nanotubes as well as physicochemical properties of the respective materials. This has determined the first studies in the field of nanochemistry. For the most comprehensive analysis of the contribution made by nanochemistry to the development of nanotechnologies, see a monograph,[1] the size-effect-based reactions and materials can be found in another monograph.[2]

It should be noted that works devoted to metal nanoparticles share a large fraction of current studies in the field of nanochemistry. This is primarily associated with the use of these particles in catalysis.[3–5] A comprehensive analysis of organic reactions that proceed in the liquid phase and involve homogeneous, heterogeneous and nanosized catalytic systems was published.[3]

For certain model catalyzed reactions, leaching of the metal atoms to the solution was shown to contribute to the generation of the activated form of a nanocatalyst. It was also noted that the catalytic activity increased with the decrease in the particle size.

The effect of the structure, morphology, size, shape, chemical composition and the oxidation state of nanoparticles on their catalytic properties was analyzed in detail.[6]

Nowadays, metal nanoparticles stabilized with organic compounds have found practical application. Methods for the synthesis of metal organosols and their potential use in the field of catalysis and surface enhanced Raman spectroscopy (SERS) were discussed.[7] The SERS method allows detection of light scattered by molecules localized near the surface of a metal nanoparticle. This has found application in the analysis of trace amounts of toxic substances.

A method was proposed for the determination of methyl parathion, an organophosphorus insecticide highly toxic for warm-blooded organisms, which is used against insects and herbivorous mites and ticks.[8] Gold nanoparticles were decorated with mono-6-thio-β-cyclodextrin (strong chemical bonds between gold and sulfur atoms form). Due to efficient formation of a 'host – guest' complex of methyl parathion with the cavity of hybridized monothiocyclodextrin – gold nanoparticle, it became possible to detect this insecticide at the picomolar level.

Methods for the synthesis and the application fields of thin films of ligand-stabilized metal nanoparticles as the sensor materials were reviewed.[9]

At present, the interest of nanotechnologies is shifted to the fields of biochemistry and medicine. Three main direc-

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tions of the active use of metal nanoparticles in medicine can be specified.[10]

Firstly, it is diagnosis of diseases in early stages and, in prospect, at the level of pathologies of individual cell. It was possible to identify proteins in blood serum, distinguish different bacterial strains and differentiate healthy and cancerous cells.[11] The technology is based on 2 nm-core gold nanoparticles that could form complexes with different fluorophores. Under the effect of appropriate substances, these complexes are disrupted and fluorescence is observed.

Yet another example is nanoparticles with discrete absorption spectra. Following special treatment, they can be used for cellular labelling (for details, see Ref. 12). The targeted delivery of nanoparticles was achieved due to their conjugation with peptides or antibodies.

The second direction is the targeted drug delivery to injured tissues. Nanotechnologies assist in solving this problem, which, in turn, allows reduction of the drug doses, enhancement of their therapeutic effect and increase in their safety.[13]

Drug delivery can become more efficient provided nanoparticles are tagged with antibodies or other recognizing elements that enable highly selective binding of nanoparticles to antigens expressed on the surfaces of injured cells. The exhaustive information on the use of nanotechnologies in oncology can be found in several reviews.[14–16]

It was shown[17] that metal-organic frameworks, a new class of hybrid materials composed of metal ions bound with one another by an organic ligand, can serve as drug carriers. Such systems are capable of biodegradation.

The third direction concerns the regenerative medicine. The latter is aimed at mobilizing the inherent properties of an organism for exerting control over such diseases as diabetes, osteoarthritis and injuries of the cardiac muscle and the central nervous system. The fundamental principle of regenerative medicine is that the biocompatible materials and the signal drug molecules capable of initiating regenerative processes at the cell level can be delivered to the affected regions.

The regenerative medicine also embraces the trend in nanotechnology that is being actively developed now aimed at imparting new physicochemical and therapeutic properties to the drugs used. The possible approaches to solving this problem include the synthesis and the investigations of properties of new polymorphic modifications of molecular crystals.[18]

Nanoparticles forming of complex organic molecule, which, in addition to carbon and hydrogen, can include atoms of oxygen, sulfur, halogens play a major role in biochemistry and nanomedicine.

The methods for the preparation and physicochemical properties of nanoparticles containing complex organic molecules are studied to an insufficient extent yet. This is partly associated with the fact that the intermolecular interactions are weaker than the interatomic ones and the size dependence of physicochemical properties of organic nanoparticles is less pronounced as compared with inorganic nanoparticles.

Nanoparticles can be considered as objects in-between the compact organic compounds and single molecules.[19]

From our point of view, the fact that the development of studies of organic nanoparticles, contrary to that of metal nanoparticles, has started only relatively recently can be explained by the following two main reasons. First, low melting temperatures and lesser thermal stability of organic nanostructures as compared with those of inorganic compounds limit the methods for their synthesis and applications. Second, it was believed that no size effect is manifested in organic nanomaterials. However, eventually it was shown that the size effect is typical of organic nanoparticles as well.

Inorganic and organic nanoparticles are both similar and dissimilar. The similarity is expressed in the size dependence of physicochemical (especially, spectral) properties. For nanoparticles of metals and inorganic semiconductors, the size effects are most strongly pronounced in the size range < 10 nm. For organic compounds, the size effects were discovered in studying the spectral properties of particles with the sizes from several tens to several hundreds of nanometres. In metals, the size effect is associated with collective electrons that can hold within the nanobulk. In organic molecules, the electrons 'pertain' to chemical bonds, the mobility of these electrons is limited, hence, the interactions that result in spontaneous formation of ensembles and favour the charge transfer are weak.

The capability for self-assembling that can be employed in designing devices for opto- and nanoelectronics has been observed so far only for the systems that comprise several cyclic and aromatic molecules. The structure and the interaction of these molecules favour the charge transfer, give rise to stacking, the appearance of excitons and shared electrons.

Yet another promising direction in the use of organic nanoparticles is associated with modification of drugs, particularly, preparation of their novel stable polymorphic forms.

The increased interest in the studies of organic nanoparticles has recently been manifested by the appearance of several reviews (*e.g.*, see Refs 20–22). Each of these publications considers a single method of fabrication of nanoparticles and summarizes the results of studies by particular research teams. In the present review, we analyzed different approaches to the manufacture and the characterization of nanoparticles of organic compounds built of several cyclic and aromatic fragments.

Such molecules are the components of drugs, various dyes. By the example of similar substances, methods for the preparation of nanoparticles are analyzed and their physicochemical properties and certain application prospects are considered.

Undoubtedly, investigations into organic nanoparticles is a promising direction and its rapid progress in inevitable.

II. Methods for the preparation of nanoparticles

Methods for the fabrication of nanoparticles can be divided into two groups:

— coarsening of original species (*i.e.*, single atoms and molecules) to form nanosized particles (the 'bottom-up' approach);

— grinding of coarse particles (molecular aggregates, powders, grains) to nanosized particles (the 'top-down' approach).

The former approach includes mainly the chemical methods for the fabrication of nanoparticles, while the latter relies on physical methods. The fundamentally different technologies often produce nanomaterials with the same chemical composition but different properties.

The synthesis of organic nanoparticles is a laborious branch of chemistry, which is poorly explored so far. The use of physical methods, *e.g.*, mechanical disintegration and laser ablation, is of limited application due to the low melting points and thermal instability of organic compounds. Only a small fraction of the known methods developed for the synthesis of nanoparticles of metals and inorganic semiconductors can be used for synthesizing organic nanoparticles. Below, the methods currently used for the preparation of organic nanomaterials are considered.

1. Physical methods

a. Mechanical grinding of the original substance

Depending on the nature of a substance and the required particle size, different kinds of mills and 'dry' and 'wet' grinding are used.[23] Dry grinding is the most popular technology that employs ball and jet mills. The surface of a mechanically ground substance is partly amorphous and has many defects, *i.e.*, it is thermodynamically activated.[24]

Grinding of Ibuprofen by the jet milling technology was described. [25] Figure 1 shows microimages of particles measuring from 1 to 7 μm, recorded using a scanning electron microscope (SEM). Nanoparticles of Fluticasone propionate with the average size of 5 μm were fabricated by the same method.[26] Fairly unstable particles are normally produced upon dry grinding. Their stabilization was achieved by adding, for instance, cellulose ethers or poly(vinylpyrrolidone),[27] which adsorbed on the newly formed surface of particles. The particles acquired a positive charge, which kept them from agglomeration.

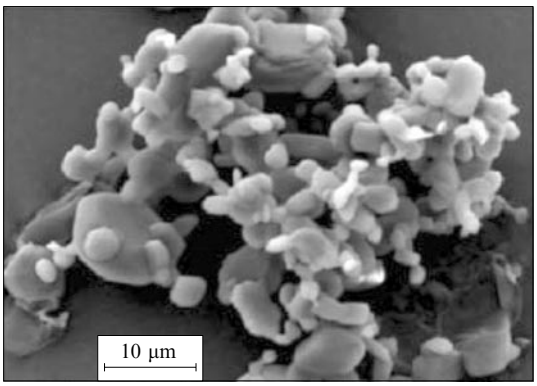


Figure 1. SEM image of Ibuprofen particles produced by mechanical grinding.[25]

In wet grinding, antisolvents are used, which prevent dust formation and the agglomeration of particles.[28] This method was used in the manufacturing of suspensions of nanosized drugs for intravenous injections.

In planetary ball mills, a drug can be ground to sizes < 0.1 μm. Thus a suspension of insulin nanoparticles (150 nm) was prepared.[29] To stabilize such suspensions, milling was carried out in the presence of special additives.[28, 30]

The following drawbacks of the mechanical synthesis can be mentioned:

— partial dissolution of the organic substance and its uncontrolled recrystallization during drying are possible;

— impurities from the mill material can inevitably get into the final product (to suppress this effect, rubber-covered glass beads were proposed as the grinding tools);[31]

— destruction of thermally unstable substances due to heat liberated during grinding;

— the presence of a relatively large number of particles measuring > 5 μm.

Suspensions of nanoparticles can be prepared by piston-gap high-pressure homogenization technology known under the 'DissoCubes' trademark. The piston motion in the cylinder creates pressure up to 2000 bar. A flow of particles mixed with water passes through a gap 3 – 5 μm wide, which occurs, according to the Bernoulli law, at a high rate.[32] A sharp decrease in the liquid flow section, *i.e.*, from the cylinder section to the gap section, results in cavitation so that the vapour bubbles first appear and then burst at the exit from the gap. The shock wave induced due to the explosion of bubbles is the factor favouring the decrease in the particle size.[33] This technology of producing nanosuspensions can be effected with APV Gaulin (Germany), AVESTIN, Inc. (Canada), GEA NiroSoavi (Italy) homogenizers.

A suspension of Atovaquone (Malorone), a drug for prevention and treatment of malaria was produced by high-pressure homogenization. The average particle size was 279 nm.[34] Amphotericin B, Itraconazole, Carbamazepine particles with the sizes of 493, 519 and 870 nm, respectively, were manufactured analogously.[35, 36]

The peculiarities of mechanical milling of substances were surveyed in a review.[25] The main drawbacks of this method is the limited possibility of a control over the size and the shape of the synthesized particles, their wide size distribution and also their irregular shape.[37]

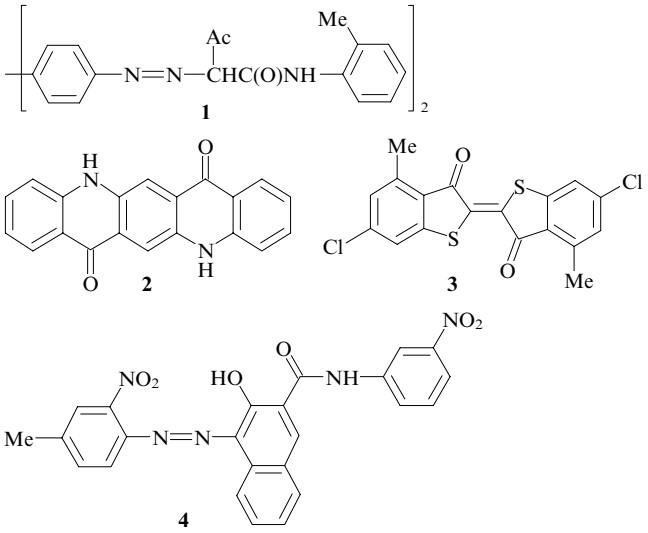
The stabilization of particles can be achieved by introducing auxiliary agents. Mechanical grinding is a convenient method for the production of nanoparticle suspensions. A large number of pharmaceutical companies use and develop various mechanical grinding technologies to improve the bioavailability of poorly soluble substances. The ease of scaling such technologies for the industrial production should be mentioned.[36]

b. Laser ablation

The first application of the laser ablation method in the formation of nanoparticles of organic compounds dates back to 2000.[38] This method is as follows: a suspension of the original microcrystalline powder is prepared in a solvent in which this substance is virtually insoluble; the thus prepared suspension is subjected to the impact of an intense laser pulse, which results in the fragmentation of grains and the transition of the original suspension to a transparent colloidal solution.[39]

The method of laser ablation of microcrystalline powders of organic compounds in a solvent has opened new prospects for the synthesis of nanoparticles. The use of lasers allows preparation of stable colloidal solutions in the absence of stabilizers.[20] By tuning the excitation parameters such as the wavelength, the laser pulse width and fluence, one can control the size and the degree of modification of the synthesized nanoparticles. Thus the increase in the laser radiation fluence results in a decrease in the nanoparticle size. The structure of formed nanoparticles of, *e.g.*, Quinacridone, depends on the laser pulse wavelength and fluence.

The method of laser ablation was used to synthesize nanoparticles of several dyes, namely, Benzidine yellow (**1**), Quinacridone (**2**), Brilliant rose (**3**) and Dark red (**4**).



Dye	**1**	**2**	**3**	**4**
Particle size /nm	59	50	40	43

The solvents used for these dyes were the 7 : 1 ethanol – water mixture for Benzidine yellow, the 39 : 1 ethanol – water mixture for Brilliant rose and Dark red and distilled water for Quinacridone. During the experiments, the solutions were thoroughly mixed with a magnetic stirrer.

Laser ablation was employed for the preparation of 20 nm particles of Indometacin and Phenitoin, a drug used for treating epilepsy.[40] In the case of a laser with the pulse width of 8 ns (nanosecond laser), the nanoparticle size was 40 – 60 nm and did not depend on the nature of substance. Using a laser with the pulse width of 150 fs (femtosecond laser), smaller particles could be synthesized.

The dependence of the nanoparticle size and structure on the laser pulse wavelength, width and fluence is related to the laser ablation mechanism. In the nanosecond region, this process was of the photothermal nature,[41, 42] whereas in the femtosecond region, it was of the photomechanical origin.[43] For nanosecond photothermal ablation in solution, the crystals of an organic compound absorbed laser radiation, which was accompanied by the local increase in temperature, compensated by cooling due to the heat transfer to the solution. The established equilibrium temperature determines the particle size. An increase in the laser radiation fluence increases the equilibrium temperature and hence favours fragmentation. For example, for a wavelength of 355 nm, the size of Quinacridone particles decreased from 120 to 50 nm as the fluence increased from 40 to 100 mJ cm^{-2}. Figure 2 shows microimages of Quinacridone particles prepared under the action of a laser pulse.

For femtosecond lasers, the multiphoton absorption induces a considerable increase in the amplitude of vibrations of lattice molecules and elevates the pressure in the irradiation zone. As the result, the mechanical fragmentation begins prior to establishment of the temperature equilibrium with the solvent, and the number of particles increases. Thus Quinacridone particles measuring 13 nm were prepared with the fluence of 40 mJ cm^{-2} and the pulse width of 150 fs.[20]

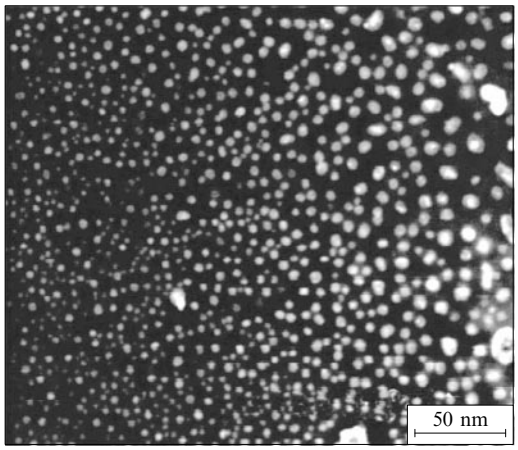


Figure 2. SEM image of quinacridone particles obtained upon laser radiation.[20]
Wavelength 355 nm, pulse duration 8 ns, fluence 100 mJ cm^{-2}.

The effect of the laser radiation fluence on the formation of different modifications of a given compound depends on the thermodynamic stability of the latter. For example, the Quinacridone β-phase is less stable than its γ-phase; therefore, the latter formed at the higher fluence.[20]

Thus, regulation of the laser radiation parameters allows the control over the size of the formed nanoparticles and production of stable concentrated dispersions of organic nanoparticles with no stabilizers.

However, the following two drawbacks of the laser ablation method deserve mention:

— nanoparticles are formed under the action of a narrow laser beam; hence, only a small amount of dispersion is formed; this implies that high power inputs are necessary for the production of considerable amounts of nanoparticles;

— intense laser radiation may cause photochemical decomposition of certain organic substances.[44]

2. Chemical methods

a. Solvent replacement

Preparation of an aqueous colloidal solution of β-carotene was described for the first time in 1965.[45] Carotene and poly(vinylpyrrolidone) were dissolved in chloroform, then chloroform was evaporated *in vacuo* to form a solid mixture of β-carotene and polyvinylpyrrolidone. Upon the addition of water to the solid mixture, an aqueous colloidal solution formed, which was called 'hydrosol' (by analogy with 'aerosol').

The hydrosol contained mainly amorphous particles of water-dispersed carotene. The average particle size in the hydrosol was 200 – 400 nm, which allowed their use for intravenous injections. Such a technology of preparation of drug hydrosols had several features. First, the precipitation required a large amount of water, and the content of water in the product was 96% – 98%. Second, considerable amounts of stabilizers are added to prevent crystallization and the particle growth. For example, in the synthesis of a cyclosporine hydrosol with the particle size of 270 nm in the presence of gelatine, the gelatine-to-cyclosporine ratio was 20 : 1.[25] The introduction of a large amount of viscous stabilizers can decrease the solubility; hence, the stabilizer

should be accurately dosed. The final stabilization was accomplished by freeze or spray drying.[25]

A new procedure that involved solvent replacement, *i.e.*, reprecipitation, was developed for the preparation of nanoparticles.[46] This procedure consists of the fast introduction of a solution of a substance in an appropriate good solvent into a large volume of a miscible poor solvent. The sudden change in the medium induces the precipitation of organic molecules.[47] The reprecipitation method was widely used for manufacture of nanoparticles of different organic compounds.[48–51] For example, perylene particles with the average size of 100 nm (Fig. 3) were obtained by pouring a 0.25×10^{-3} M perylene solution in acetone to water with vigorous stirring.[52]

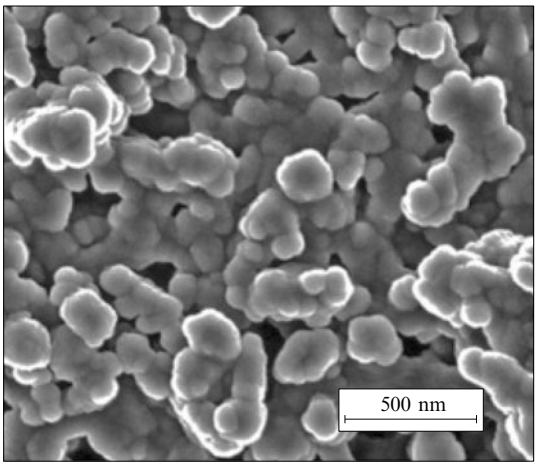
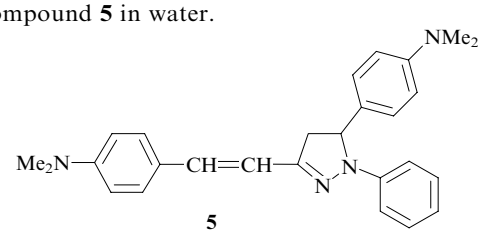


Figure 3. SEM image of perylene particles synthesized by the reprecipitation method.[52]

Nanoparticles of 5-(4-dimethylaminophenyl)-3-(4-dimethylaminostyryl)-1-phenyl-2-pyrazoline (**5**) were prepared by adding an ethanol solution of this compound (1.0×10^{-3} M) to water with vigorous stirring. Aggregation began immediately to form a dispersion of nanoparticles of compound **5** in water.

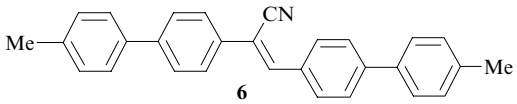


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The size of the obtained nanoparticles can be controlled by changing the volume of the added ethanol solution of compound **5** and varying the temperature. Thus the addition of 40 and 100 μl of the ethanol solution to 10 ml of water resulted in 50- and 105-nm nanoparticles of compound **5** at 25 °C and 90- and 190-nm nanoparticles at 50 °C, respectively.[51]

Reprecipitation of 1×10^{-3} M acetone solution of 5-(4-dimethylaminophenyl)-3-naphthyl-1-phenyl-2-pyrazoline (100 and 50 μl) with water at 25 °C afforded nanoparticles measuring 65 and 40 nm, respectively.[53]

In a similar way, nanopartices of *trans*-1-cyano-1,2-bis(4′-methylbiphenyl-4-yl)ethylene (**6**) were prepared.



6

Tetrahydrofuran was used as the solvent and water served as the antisolvent. According to data from emission scanning electron microscopy, nanoparticles of compound **6** represented spheres with the diameter of 30–40 nm. The suspension of nanoparticles was transparent without any sediment and stable for more than three months.[49] It was shown[54] that hydrophobic molecules containing the polar C=O groups were stable in water for more than a year with no surfactants.

Using the reprecipitation method, with dimethyl sulfoxide as the solvent, particles of the dye indigo blue measuring 11–17 nm were obtained.[55]

The nanoparticle synthesis by solvent replacement occurs under mild conditions, which allows fabrication of nanoparticles of thermally unstable compounds.[52] This method is relatively simple and accessible. However, its drawbacks include low production performance.[56] Very dilute solutions of nanoparticles are obtained, because it is the millimolar concentrations of the organic compounds that are normally added to large volumes of antisolvents. Second, this method cannot be used for substances poorly soluble in organic solvents (*e.g.*, for pentacene).

b. Chemical reduction in solution

Chemical reduction in solution is one of the most popular methods for the production of nanoparticles of different metals and semiconductors.[57] So far, this is not widely used for preparing organic nanoparticles; however, it was employed in some special cases.

For example, we consider the synthesis of perylene (Pe) nanoparticles. This is based on the reduction of perylenylium perchlorate with the bromide anions in the presence of cetylammonium bromide (CTA^+Br^-) in acetonitrile.[58]

Perylene perchlorate was synthesized by the reaction:

$$2\,Pe + 2\,AgClO_4 + I_2 \longrightarrow 2\,Pe^+\,ClO_4^- + 2\,AgI.$$

The reduction of perylene perchorate proceeded according to the equation:

$$2\,Pe^+ClO_4^- + 2\,CTA^+Br^- \longrightarrow 2\,Pe + Br_2 + 2\,CTA^+ClO_4^-.$$

As a result, perylene nanoparticles measuring from 25 to 90 nm were obtained. It was noted that the changes in the cetylammonium bromide-to-perylene perchlorate molar ratio resulted in perylene nanoparticles of different sizes. Thus for the ratio 0.2–0.3, particles of 25 nm were obtained. As the molar ratio increased, the particle size also increased.

The way of injection of the reducing agent strongly affected the shape of perylene nanoparticles. Its dropwise addition resulted in single spherical nanoparticles, whereas its addition in one portion led to self-assembling of nanoparticles to afford nanorods.

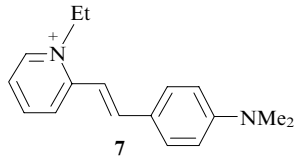
By an example of perylene, the following advantages of the method of reduction in a homogenous solution were revealed:

— separation of nucleation and particle growth steps;

— the possibility of control over the particle size by varying the substance concentration and the mode of its injection.

c. Ion association

Ion association in aqueous solution was used for the preparation of nanoparticles of pseudocyanine dyes.[59] The essence of this method can be explained for the synthesis of a cationic styryl dye (**7**), 2-(4-dimethylaminostyryl)-1-ethylpyridinium cation.



7

Compound **7** tends to be associated with different hydrophobic borate anions in the presence of a neutral stabilizer, polyvinylpyrrolidone.[60] Fast injection of a solution of 2-(4-dimethylaminostyryl)-1-ethylpyridinium iodide to a solution of sodium tetraphenylborate afforded pure suspension of nanoparticles of compound **7** with the size from 30 to 100 nm.

The method of ion association employs no organic solvents. The particle size can be controlled by varying the cation-to-anion molar ratio.[61]

d. Synthesis of nanoparticles in water – oil emulsion

Nanoparticles were synthesized in water – oil emulsions containing a solute in a volatile solvent. Evaporation of the solvent affords nanoparticles with sizes comparable with the emulsion drops. Emulsification required the use of special equipment to achieve the needed drop size. Nanodrops were prepared by high-pressure homogenization and sonication.

From microemulsions containing sodium dodecyl sulfate as the surfactant, nanoparticles of Propylparaben with the sizes of 40 – 70 nm were obtained.[62]

A version of producing nanoparticles in a stabilizer-free oil-in-water emulsion was proposed.[56] Figure 4 illustrates a possible mechanism of the organic nanocrystal fabrication using the emulsion method. First, an emulsion of the target substance in an organic solvent was prepared at elevated temperature. Its subsequent cooling to room temperature brings about nucleation and the crystal growth inside the emulsion. The formed nanoparticles are transferred into the water phase and dispersed by a mechanical method, *e.g.*, by sonication. Thus nanoparticles of tetracene measuring 85 nm and anthracene measuring 75 nm were prepared.

e. Photochemical method

A new method was proposed for producing organic nanoparticles consisting of molecules of acridine dyes.[63] It is based on a photochemical reaction of tetrabromomethane and di-*p*-tolylamine in polystyrene films. The films were irradiated with light of different wavelengths and intensities in the presence of tetrabromomethane vapour. The reaction occurs at the polymer/vapour interface, which allows producing the dye nanoparticles in the fixed site on the polymer surface.

The size and the number of nanoparticles could be controlled by varying the intensity of the light flux, its spectral composition and the duration of irradiation. Illumination with an incandescent lamp produced 100-nm particles. For the light flux of higher intensity, the argon laser was used. For the irradiation times of 20 s and 5 min, the average particle sizes were 40 and 80 nm, respectively.

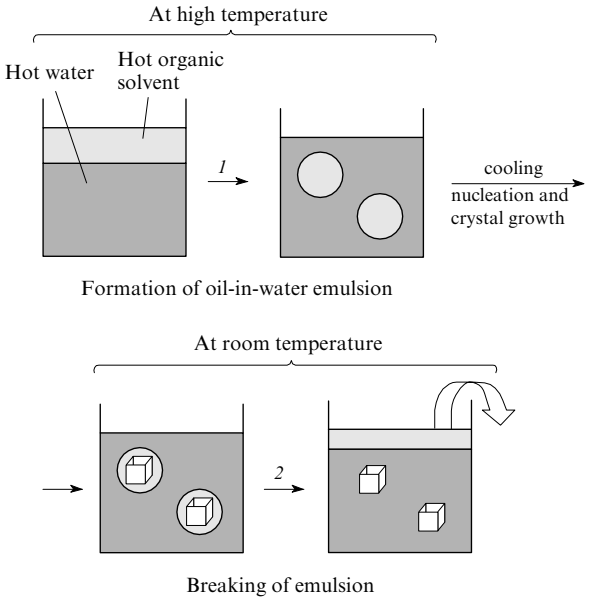


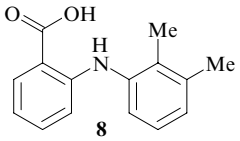
Figure 4. Schematic model of the organic nanocrystal fabrication by the emulsion method of nanoparticles by the emulsion method.[56] (*1*) Preparation of the oil-in-water emulsion by stirring, (*2*) transfer of nanoparticles into the water phase, for example, by sonication.

An interesting experimental fact is that micropores formed in the polymer film. The micropore size could be regulated by varying the parameters of the photoimpact.

f. The use of supercritical fluids

At present, the use of different substances in subcritical and supercritical states for the production of nanoparticles of organic compounds is being intensively developed. The supercritical fluid (SCF) technologies have considerably extended the potential of preparation of organic nanoparticles. The classification of SCF technologies can be found in several reviews.[64 – 66] A chemical compound in the supercritical state may be used as both the solvent and the precipitant.[67] Carbon dioxide was used most often as the supercritical solvent. It represents a non-inflammable, cheap, non-toxic gas and is characterized by mild conditions of the transition to the critical state ($T = 304$ K and $P = 73.8$ atm).[68]

Supercritical fluids as solvents were successfully used in a version of rapid expansion where the saturated solution of a compound in a supercritical fluid is sprayed through a nozzle. As the pressure drops, the solvent passes to the gaseous phase and the substance is precipitated to form fine aerosol. This method was used to produce, at a pressure of 220 – 450 atm and a temperature of 308 – 348 K, 100-nm spherical nanoparticles of a local anaesthetic, Lidocaine.[67] By a similar procedure, nanoparticles of mefenamic acid (**8**) measuring 880 nm were fabricated.[69]

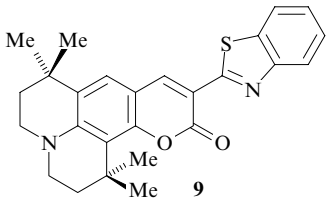


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A variation of the rapid expansion process is a rapid expansion of a supercritical solution with the target substance into a liquid solvent. Thus Ibuprofen particles measuring 40 nm were stabilized in a solution of sodium dodecyl sulfate.[70]

In another example, the supercritical fluid containing the dissolved compound was sprayed into water containing the surfactant Twin-80 to produce cyclosporine particles measuring 500 nm.[68]

Nanoparticles of the dye C545T (**9**) measuring 5–15 nm was produced using supercritical carbon dioxide.[71]



9

The drawback of the method under consideration is that the range of compounds readily soluble in supercritical carbon dioxide is limited.

Nanosizing of insoluble or poorly soluble substances can be effected where the fluid performed the functions of the precipitant. For the dissolution of such substances, organic compounds are used that are soluble either completely or partly in the supercritical fluid. A saturated solution of the target compound in the organic solvent was sprayed under controlled conditions through a nozzle into a vessel containing the fluid where the compound crystallized due to the abrupt decrease in the solubility to afford micro- and nanoparticles. It was noted that the residual amounts of organic solvents could contaminate the final product.[67]

The following procedures were developed in which the supercritical solvents could be used as the medium for the precipitation of the target micro- and nanoparticles:

— precipitation in a gaseous antisolvent [Gas Anti-Solvent (GAS)];[72]

— precipitation in a supercritical antisolvent Supercritical Anti-Solvent (SAS)]; this procedure was used for producing tetracycline particles measuring 150 nm;[73]

— dissolution of a fine dispersion in a supercritical fluid [Solution Enhanced Dispersion by Supercritical Fluids (SEDS)]; Sulfathiazole particles measuring ~200 nm were prepared using this procedure;[74]

— supercritical extraction [Aerosol Solvent Extraction System (ASES)].

As an example, let us consider supercritical extraction of a glucocorticosteroid Budesonide. The steroid solution in dichloromethane was sprayed into a large volume of SCF (carbon dioxide) for 1 h. Dichlorometane is soluble in SCF and hence is extracted, while the insoluble steroid forms the solid phase.[75] Figure 5 shows a microimage of Budesonide nanoparticles.

The merits of the SCF technologies is their environmental safety in the case of SCF-soluble substances; their drawbacks is the contamination of the final product with the solvent in the case of production of nanoparticles of substances insoluble in SCF as well as the sophisticated instrumentation required for this process and, as a consequence, high cost of the final product.[76] Certain progress was achieved in solving the problem of scaling the SCF technologies to make them suitable for industry.[77,78]

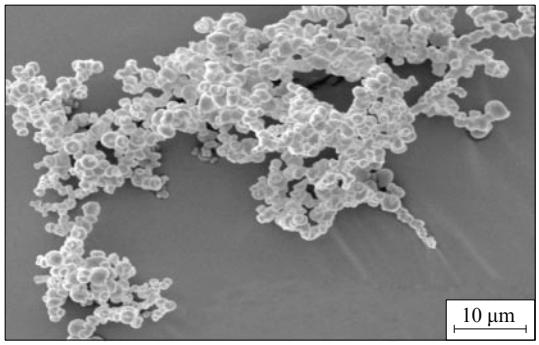


Figure 5. SEM image of Budesonide particles prepared by supercritical extraction.[75]

g. Cryochemical synthesis and modification of nanoparticles

Cryochemistry studies the reactions proceeding at low (77 K) and ultra low (4 K) temperatures. In this temperature range, unusual chemical transformations involving free radicals, ions, unstable molecular complexes were observed.[79] New mechanisms of traditional classic and model reactions of the halogen and hydrohalide addition to double bonds occurring at low temperatures were discovered.[80] The low-temperature limit for the chemical reaction rate was determined and the presence of the tunnelling mechanism was demonstrated for reactions at ultra low temperatures.[81]

The cryochemical synthesis of nanoparticles of organic compounds is based on a well-balanced combination of cold and heat; its peculiarities were considered in Ref. 82. Low temperatures are used to avoid uncontrolled changes in the intermediate and target products and to control the properties of the resulting materials. This method involves deep freezing of solutions of substances which leads to fast solidification of both the solvent and the solute.[83] The obtained product in the form of cryogranules was subjected to freeze-drying (cryodrying) or cryoextraction. The cryodrying includes the following stages: freezing, primary drying and secondary drying. The freezing rate affects the subsequent sublimation and the properties of the final product. The critical freezing rate was found below which the particles tend to aggregate.[84] Cryochemical technology allows production of diverse materials (Fig. 6).

As a rule, the contemporary drugs represent complex organic compounds, of which many are virtually insoluble in water. The poor solubility limits the modes for drug administration into the organism and affects the kinetics and the mechanisms of their targeted delivery, metabolism and excretion.

A new method was proposed for modifying and dispersing crystalline powders of drugs with recourse to low temperatures.[85,86] The method relies on the non-equilibrium metastable states of systems formed as a result of vapour deposition onto a cold surface, which is followed by heating to room temperature (Fig. 7).

The fundamentals of this method were developed when studying different chemical transformations of organic compounds at low temperatures.[87,88]

By varying the condensation and heating conditions, one can control the parameters of processes and the properties of products. Two methods were developed for drug

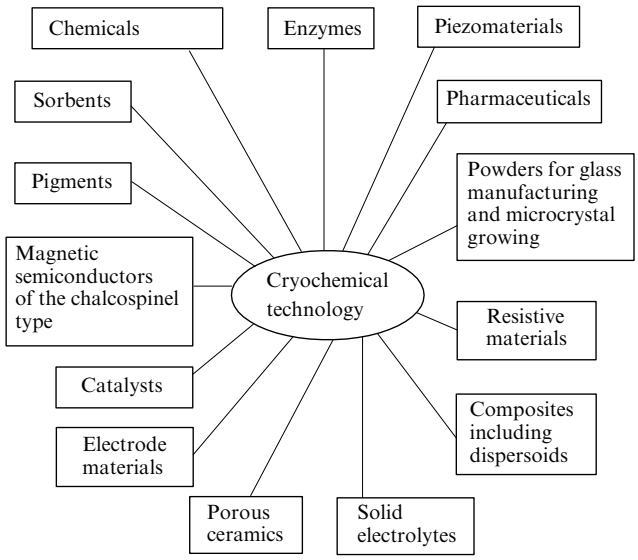


Figure 6. Materials produced by cryochemical technology.[82]

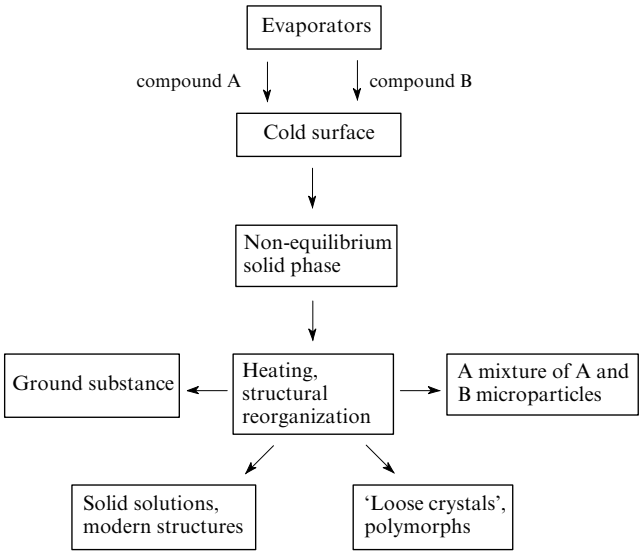


Figure 7. A scheme of possible transformations of one or two organic compounds in the condensation and heating.

modification. One of them is based on vaporization and carrying of the substance by a heated gas stream followed by its condensation on a cold surface. The other method is based on the vaporization and condensation in vacuum. The proposed methods were used for modifying and dispersion of the following drugs: Carvedilol, Moxonidine, Glibenclamide, Fluticasone propionate, Gabapentin, androstenediol, Piroxicam. The majority of drugs were virtually insoluble in water.

An amorphous form of a cardiac drug, Carvedilol, was synthesized by in-flow modification.[89] According to data from optical microscopy, the size of the original Carvedilol particles was 10–15 μm; the average particle size of the cryomodified drug was 1 ± 0.1 μm, the minimum size was 0.5 μm. The biological and medicinal trials pointed to an increase in the amorphous drug activity with the decrease in the particle size.

The jet method in an inert gas flow was used for studying the modification of the hormone Δ^5-androstene-3β,17β-diol as a radioprotector. According to IR spectroscopic data, the initial and the modified forms of androstenediol were similar. According to XRD studies, the modified drug represented a crystalline monohydrate of androstenediol. The particle size of the original drug varied from 3 to 300 μm. Figure 8 shows the size distributions of the original and the modified particles. The average size of androstenediol particles decreased to 200 nm and the minimum size decreased to 100 nm.

As the particles size decreased to nanometres, the mass rate of dissolution increased more than 1.5-fold for the same temperature and sample mass.

For the antiepileptic agent, Gabapentin, the use of the method of vacuum sublimation–condensation made it possible to produce three forms of which one was obtained for the first time.[90] The particle size of the cryomodified drug was 0.5 μm.

The method of vacuum cryomodification was developed for sublimation of compounds that are non-volatile and chemically unstable at elevated temperatures.[91] The evaporation was carried out by pressing mechanically a thin layer of the substance to a heated metal grid. The condensation could be accomplished onto the walls of a polished copper

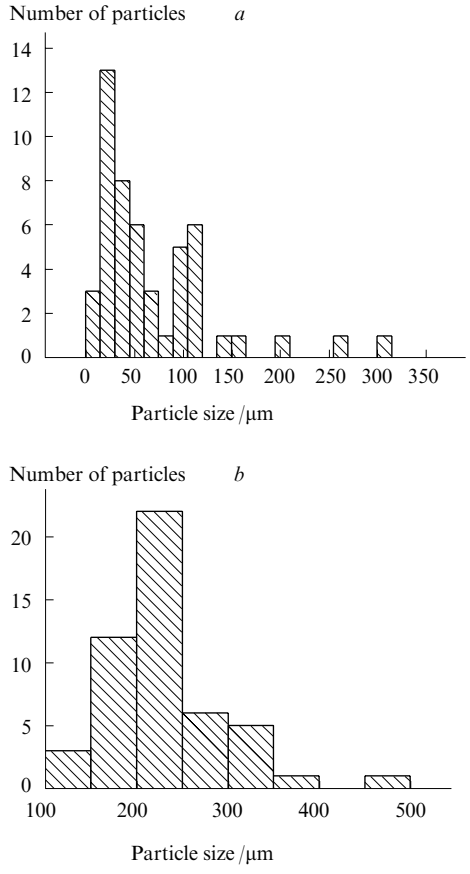


Figure 8. Histograms of the size distribution of Δ^5-androstene-3β,17β-diol particles according to the data of scanning electron microscopy in the original (*a*) and modified (*b*) substances.

cube cooled by liquid nitrogen; simultaneously, IR spectra of the condensate could be recorded.

The discussed methods of cryomodification had distinctive features. The transfer of the substance to the gas phase and the use of liquid nitrogen ensured that the final product was obtained from its molecular and non-equilibrium state. Using controlled heating, it was possible to change the size and the structure of modified particles and obtain their new forms.

Micronization of drugs was carried out in the absence of solvents. Cryochemical methods made it possible to modify the substances due to the introduction of auxiliary agents used in the drug synthesis.

At low temperatures, a new modification of 7-bromo-5-(2-chlorophenyl)-1,3-dihydro-2*H*-benzodiazepin-2-one (Phenazepam),[92] one of the most efficient psychotropic agents used most widely in the medical practice, was obtained (Fig. 9).

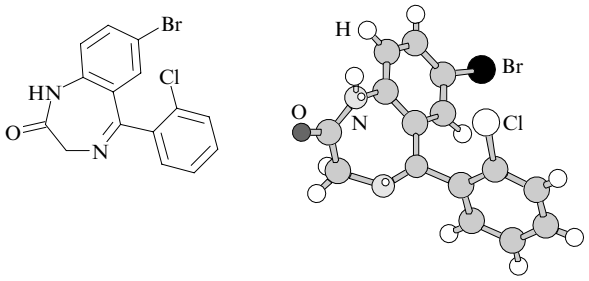


Figure 9. Phenazepam structural formula and a view of its molecule with the optimized structure.

A new modification of Phenazepam was prepared in a unit that allowed transfer of a crystalline substance into the gas phase, which was followed by its condensation in an inert gas flow onto a surface cooled with liquid nitrogen. NMR-spectroscopic examination of solutions of the original Phenazepam and its cryomodification in dimethyl sulfoxide-d_6 has shown that the chemical composition of the Phenazepam molecule remained unchanged.

A comparison of the results of XRD analysis of modified Phenazepam with the data from the Cambridge Crystallographic Data Centre revealed the appearance of a new crystalline modification, β-polymorph. The lattice parameters of the cryomodified monoclinic Phenazepam, $C_{15}H_{10}BrClN_2O$, were are follows: $a = 14.8006(19)$, $b = 11.6756(14)$, $c = 8.4769(9)$ Å, $\beta = 93.679(17)^\circ$, $V = 1461.8(3)$ Å^3, $\rho_{cal} = 1.59$ g cm^{-3}, $Z = 4$, space group $P2_1/c$. The average particle size of the β-polymorph of Phenazepam was 55 ± 12 nm according to XRD data and 30–120 nm according to the transmission electron microscopy (TEM) data, *i.e.*, the results obtained by these two methods were mutually consistent. In water, the β-polymorph dissolved faster by a factor of 3.9 as compared with the original Phenazepam.

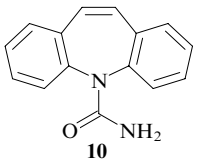
The particle size of drugs affected their solubility, dissolution rate, bioaccessibility and metabolism. The mode of administration of a drug into the organism is chosen depending on the particle size.

Biopharmacological *in vivo* trials of cryochemically modified Phenazepam have shown that the new modification retained the advantages of the original drug while the side effects decreased by 40%.

In pharmacology, keen attention is paid to the synthesis and the use of new crystalline polymorphs of drugs. This is associated with the fact that different crystal systems with different unit cells (polymorphs) obtained from the same elements possess different physical and chemical properties and can have different therapeutic action. The state of the art in the studies of polymorphism and numerous examples of the use of this effect in pharmacology were described in a monograph.[93]

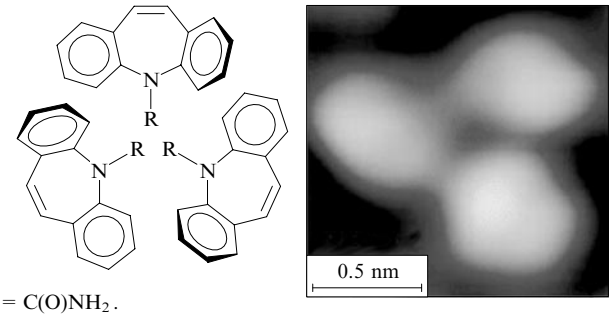
Sublimation of drugs followed by their condensation onto cold metal surfaces was employed [94] in the synthesis of polymorphic modifications of the antiepileptic drug, Carbamazepin (**10**). The drug was condensed on the Au(111) and Cu(111) surfaces at 80 K and its structure was studied at the same temperature by the scanning tunnelling microscopy.

On the Au(111) surface, compound **10** formed the molecular structures different from those observed in three-dimensional crystals, namely, trimers were formed as the result of intermolecular hydrogen bonding and interaction with the metal (Fig. 10). In neither of the polymorphs known, such formations have ever been observed.



10

The nature of metals was shown to influence the chirality and the density of packing of two-dimensional molecular structures.



R = C(O)NH$_2$.

Figure 10. A scheme of formation of Carbamazepin trimer and its STM image on the Au(111) surface.

The obtained results can potentially be used for monitoring the polymorph formation. However, in the authors' opinion it is necessary to elucidate whether the synthesized two-dimensional structures can act as the templates in the formation of three-dimensional crystalline particles.

III. Properties and application of organic nanoparticles

In the Introduction to this review, the similar and dissimilar properties of nanoparticels of metals and organic compounds were outlined and certain application fields of organic nanoparticles were considered. In the present Sec-

tion, the spectral and other properties of the latter are analyzed in more details.

The dependence of the Stokes shift in the molecular spectra on the size of organic particles was revealed.[95] The restriction for the exchange interactions in organic nanoparticles brings about an increase in the non-linear optical characteristics.[96] The dependence of the melting temperature on the particle size was demonstrated.[97] A substantial difference in the optical and electronic properties of organic nanomaterials from the properties of nanomaterials based on metals and inorganic substances is associated with the presence in the former of weak intermolecular interactions such as the van der Waals forces and $\pi-\pi$-conjugation.

The dependence of optical properties on the size of organic nanoparticles, which ranged from several tens to several hundreds of nanometres,[20] was considered by many authors. The optoelectronic properties of organic nanoparticles are governed by the charge-transfer excitons and the Frenkel excitons with small radii. The effect of exciton localization was rationalized.[51]

Figure 11 shows UV spectra of nanoparticles of compound **5** in water and in a dilute aqueous solution of ethanol. In solution, the following three absorption bands appear: the first is associated with the phenyl radical (P_{Ph}) and the other two are associated with the $n-\pi^*$- ($P_{n-\pi^*}$) and $\pi-\pi^*$-transitions ($P_{\pi-\pi^*}$) of the pyrazoline ring. As the particle size increased from several tens to a hundred of nanometers, the P_{Ph} and $P_{\pi-\pi^*}$ bands shifted in the long-wavelength direction. Presumably, the observed bathochromic shift is the result of the increased overlap of π-orbitals of the pyrazoline ring and the strengthening of interactions between the molecules of compound **5** with the increase in the particle size.[51]

The emerging absorption is explained by the appearance of charge-transfer excitons (P_{CT}) throughout the extended crystal structure of aggregates of molecules **5** closely stacked in nanoparticles.

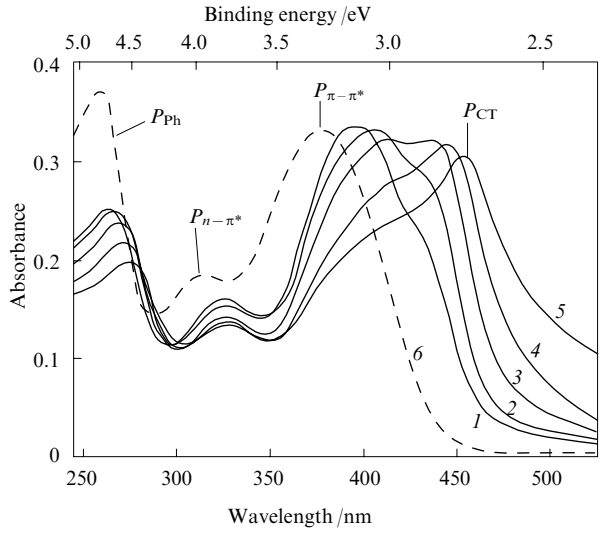


Figure 11. UV-Vis absorption spectra of dispersions of nanoparticles of compound **5** in water (*1–5*) and of a solution ($C = 1 \times 10^5$ M) in ethanol (*6*).[51]
Particle size /nm: (*1*) 20; (*2*) 50; (*3*) 105; (*4*) 190; (*5*) 310.

An interesting phenomenon of multiple luminescence is manifested in nanoparticles of 1,3-diphenyl-5-pyrenyl-2-pyrazoline (**11**). This compound contains two sterically separated chromophore fragments, namely, pyrene and pyrazoline. In solution, the emission is associated only with the pyrene fragment, whereas in a solid crystal, this was exclusively due to the pyrazoline fragment. However, in nanoparticles of compound **11**, the multiple emission of radiation from pyrene, pyrazoline fragments and, additionally, from the charge-transfer complex between the pyrene and pyrazoline fragments was observed.[98] It was shown that with the increase in the particle size, the luminescence decreased.

Systematic studies of pyrazoline derivatives were carried out.[99] It was shown that the fluorescence spectra of 5-(2-anthryl)-1,3-diphenyl-2-pyrazoline nanoparticles differed from the spectra of solutions and crystals of this compound.

Guanosine or guanine (G) derivatives with oligo(*p*-phenylene-vinylene) substituents in position 8 prepared by a Pd-catalyzed cross-coupling form hydrogen-bonded self-associates.[100] In the absence of an alkali metal salt, they undergo self-assembly with possible predominance of G-based tetramers (Figs 12*a* and 13).

In the presence of alkali metal salts, the octamer can be formed as a result of cationic-dipolar interactions (Fig. 12*b*). The assembly of stable disk nanostructures with the diameter of 8.5 nm and the height of $\sim$1.5–2.0 nm was observed.

Fluorescent organic nanoparticles were used, for instance, as the organic light-emitting diodes (OLED).[101] The efficiency of fluorescence of organic chromophores decreased in the solid state as a result of concentrational quenching. For certain fluorophores, the aggregation phenomenon was observed, which was accompanied by intensification of fluorescence rather than its quenching.[102, 103] For example, the fluorescence of solid *trans*-1,2-bis[4-(carbazolyl)phenyl]-1,2-dicyanoethylene nanoparticles was more intense as compared with a solution of this compound.[104] The photoluminescence of solid nanoparticles of compound **6** was 700 times (!) more intense than that of its solution.[49]

A new class of stable highly soluble substances, *viz.*, donor-acceptor carbazole derivatives, was described in detail.[105] The dependences in their physicochemical properties on the change in the acceptor group was studied as well as their photophysical properties in different solvents. In tetrahydrofuran–water mixtures, organic nanoparticles are formed with the size of $\sim$250 nm. Presumably, such particles could be used as OLED in dye-sensitized solar cells or the Gretzel cells.

Light-emitting diodes were mainly used in the design of devices for data representation in the production of thin full-colour displays. The full-colour displays based on light-emitting diodes are commercially available. However, no cheap displays have been developed so far with the sizes comparable with those of the modern liquid-crystalline displays. The main difficulty faced by researchers was associated with the non-uniformity of light-emitting organic substances applied onto the screen surface. The difference in the organic film thicknesses led to non-uniform luminescence and had an adverse effect on the quality of colour reproduction by these displays. An unexpected and interesting solution to this problem is based on the incorporation of

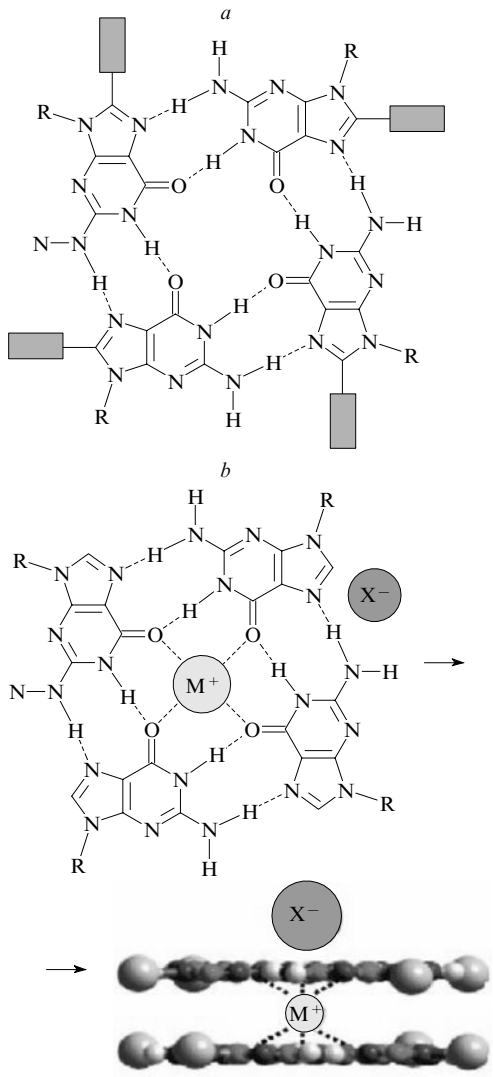


Figure 12. A model of self-assembly of guanine derivatives as a result of formation of hydrogen bonds (*a*) and in the presence of alkali metal cations (*b*).[100]
Initially, the tetramer was formed as the result of hydrogen bonding. Four carbonyl groups in the centre of this structure formed a small cavity, which can be occupied by a metal cation. The formation of the complex proceeded more efficiently if a similar tetramer was added on top. In this case, octamers were formed in which the metal cation was coordinated to eight carbonyl groups from two guanine tetramers. R is ribose, M^+ is a metal cation, X^- is an anion.

organic field transistors into the displays.[106] Each of such transistors controls an individual pixel.[107] By controlling the current, it is possible to obtain the screen glow uniform over the whole surface, which required no substantial complications in the technological instrumentation for the selective deposition of light-emitting substances.

When analyzing the properties and the application fields of organic nanoparticles, special attention should be drawn to quasi-one-dimensional (1D) organic materials in the form of nanotubes, nanoribbons and nanowires. It is believed that such materials should have great influence on the development of microoptoelectronics of the next generation.[108]

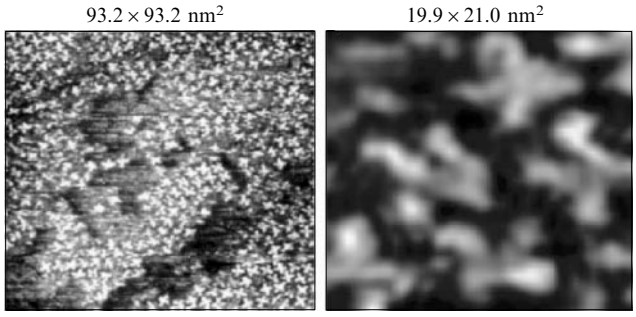
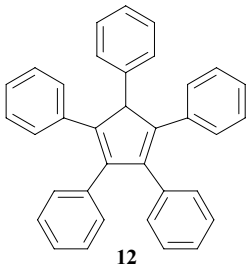


Figure 13. STM images of nanoparticles of a guanine derivative at different magnifications.[100]

Several methods were proposed for the preparation of 1D materials: by self-organization in solution,[109–112] template synthesis[113–115] and physical vapour deposition.[116] Quasi-one-dimensional organic materials exhibit interesting optoelectronic properties. First of all, mention should be made of their inherent multicolour or the so-called red-green-blue (RBG) emission, which is applied in displays and screens. Such a colour combination has usually been obtained by mixing different dyes each emitting its own colour. Recently, the multicolour emission has been observed for one substance, 1,2,3,4,5-pentaphenylcyclopenta-1,3-diene (**12**).[117]



12

Under the action of light with the corresponding wavelengths, the blue, green and red emission was observed for the 1D structure of compound **12** (Fig. 14).

Yet another peculiarity of organic 1D nanostructures is associated with their properties of optical conductors. For example, 9,10-bis(phenylethynyl)anthracene nanotubes with the diameter of 690 nm and the length of 2.5 μm demonstrated the characteristic yellow emission with very bright luminescent sites at both ends of the nanotube and the relatively weak emission of the whole nanotube (Fig. 15).[118]

Finaly, yet another significant property of organic 1D materials is the adjustable luminescence of binary nanowires. This effect was described in detail for nanowires of 1,3,5-triphenyl-2-pyrazoline with an addition of 9,10,11,12-tetraphenylnaphthacene (rubrene). It was observed that with the increase in the rubrene content, the emission colour changed from blue to orange.[119]

Fluorescent nanoparticles of organic compounds can be used for detecting different substances. Thus nanoparticles of 1-aminopyrene (**13**) are applicable for the quantitation of nitrites.

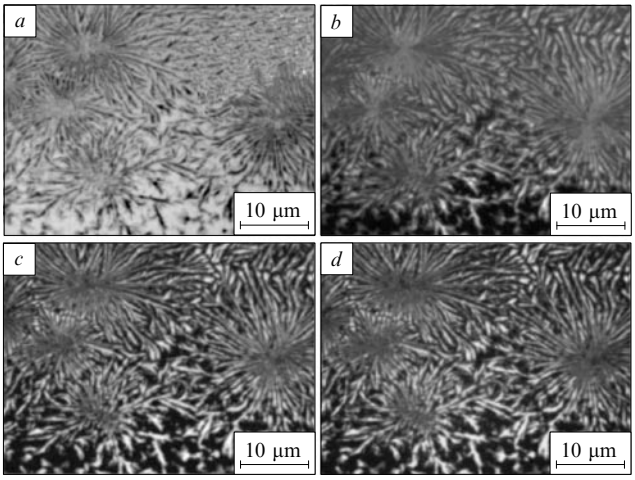


Figure 14. Photomicrographs (fluorescence microscopy) of nanoribbons of compound **12**.[117]
(*a*) Bright-field image; irradiation with UV light with the wavelength of 30–380 (*b*), 460–490 (*c*), 520–550 nm (*d*).

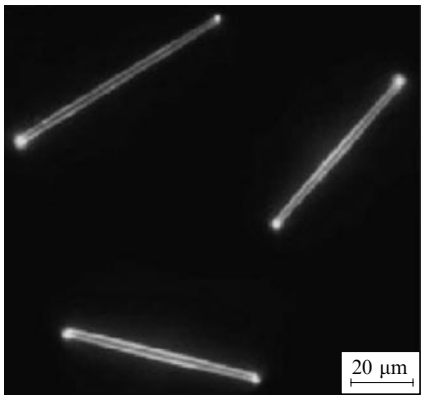
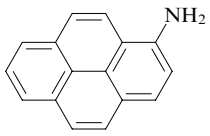


Figure 15. Photomicrograph (fluorescence microcopy) of nanotubes of 9,10-bis(phenylethynyl)anthracene irradiated with UV light of the wavelength 460–490 nm.



13

The fluorescence intensity is quenched by nitrites when involved in diazotization reaction, and the fluorescence extinction is proportional to the nitrite concentration.[120]

Nanoparticles of organic compounds demonstrate a great application potential in 'green' chemistry and chemical biology. They easily form aqueous dispersions, which makes it possible to obviate toxic solvents in carrying out chemical reactions.[121] The preparation of aqueous solutions of organic substances as well as monitoring the reactions with living cells in these solutions required the use of detergents. Nanoparticles as such can react with cells and hence require no detergents.

Production of drug nanoparticles is one of the main directions in the preparation of new highly efficient formulations. Micro- and nanoforms of drugs exhibit unique properties and open up new promising approaches to the treatment of different diseases. Solubility of drugs is one of the properties that determine their efficacy.

The calculated and measured solubility values sometimes differed from 2–3-fold to 20-fold.[122] Such a difference can be associated with the fact that solubility depends on the particle size and shape and also on the presence of a charge that can affect both solubility and nucleation.

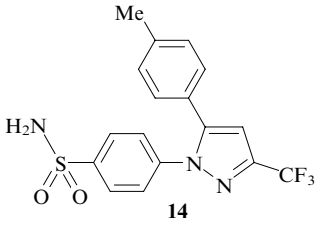
The properties determining the solubility can be divided into two groups, namely, intrinsic of coarse compact compounds and nanosized compounds. For coarse particles with the small surface-to-volume ratio (S/V), the important properties are the lattice enthalpy or the entropy and the properties pertaining to the solute–solvent interaction, such as the surface roughness, the charge, *etc*. For nanoparticles with the larger S/V ratio, it is the properties affecting the nucleation and the particle growth, the state of particle surface and its fractal dimensionality that are important.[123]

Theoretical estimates show that for particles measuring < 100 nm a considerable increase in solubility as compared with coarse particles could be expected. The classical Ostwald–Freundlich equation proved to be insufficient to comprehensively describe the nanoparticle solubilities.

The possibility of preparing nanosuspensions of poorly soluble substances is considered as an attractive merit of such drugs.[124]

The modification of the nanoparticle surface can be used in developing new methods of dissolution of poorly soluble substances. Thus the dissolution rate of Meloxicam nanoparticles is 6 times higher than that of the original drug.[125]

The drug Celecoxib (**14**) poorly soluble in water is used for treating rheumatoid arthritis, osteoarthritis and psoriatic arthritis.



14

Production of amorphous nanoparticles of this drug measuring 17 nm increased its dissolution rate 10-fold.[126]

The kinetics of nanoparticle nucleation by the example of four drugs insoluble in water was analyzed.[127] The effect of sonication and of hydroxypropylmethylcellulose (HPMC) on the particle deposition in the presence of an antisolvent (water) was studied. The antifungal drug Itraconazole, the antibiotic griseofulvin, the non-steroidal anti-inflammatory drug Ibuprofen and the antibacterial drug Sulfamethoxazole were tested, which made it possible to assess how the physicochemical properties affect the nucleation rate and the particle size determined by the light scattering technique. The analysis of the results was performed within the framework of the theory of homogeneous nucleation, which allowed the contributions of kinetics and thermodynamics to be separated and the particle size to be taken into account. It was found that sonication and the addition of HPMC accelerate nucleation. Sonication favoured the increase in the water molecule diffusivity. This

increased the contribution of kinetic factors into the nucleation acceleration. The addition of HPMC reduced the solution viscosity and, hence, the contribution of the kinetic component.

However, the addition of HPMC also reduced the surface tension and decreased the contribution of thermodynamic factors. Hence, the use of HPMC favoured a decrease in the energy barrier to nucleation and its acceleration. It was noted the decrease in this barrier was more pronounced for hydrophobic molecules such as Intraconazole as compared with other molecules, *e.g.*, Sulfamethoxazole. This is associated with the lower solubility of the former as compared with that of hydrophilic compounds like Sulfamethoxazole. The differences in the nucleation rates affect the particles involved in this process the sizes of which depend on the properties of the original substance such as the wettability for solid particles and the interfacial tension.

The therapeutic effect of drugs poorly soluble in water is apparently low. As a result, they have to be used in large doses, which entails undesirable side effects. This problem is especially important for drastic anticancer, hormonal, anti-inflammatory and antifungal drugs and antibiotics. Nanotechnologies can provide a decrease in the therapeutic doses of drugs with the retention of their therapeutic effect, which would be favourable for reducing the size effects.

Moreover, micronization up to nanosizes determines the development of drugs for the aerosol, intravenous and intramuscular applications. For example, an aerosol of nanoparticles (3–200 nm) of a non-steroidal anti-inflammatory drug Indometacin was fabricated. The trials in mice have shown that this aerosol was more efficient than the conventional oral form.[128] Other applications of nanoparticles in medicine have been considered elsewhere.[129] The wider use of nanoparticles in medicine was partly limited by their relatively high cost and the insufficiently studied mechanisms of their interaction with living cells and tissues of the organism.

Nanoparticles can increase the selectivity of drug action, its dissolution rate, adsorption and bioaccessibility. The selectivity at the delivery appears due to specific interaction with certain tissues. Nanoparticles are capable of decreasing the lifetime of small peptides and nucleic acids and affect the prolongation of the pharmacological action.

However, new side effects may be associated with the nanoparticles. Pharmacokinetic profiles of original drugs usually differed from those of their nanoencapsulated forms. When using nanoparticles, it is necessary to simultaneously monitor the positive and the negative effects of the pharmacokinetics. The pharmacokinetic studies is the main criterion of taking into account the effects of size, charge, shape, and the surface and chemical properties that appeared when drugs consisting of nanoparticles encapsulated into liposomes or other carriers are used.[130] The major problem of the use of nanoparticles is ensuring their interaction with the target cell.

Different strategies of how to use nanoparticles for improving the accessibility of drugs are being developed. However, besides hypothermia, none of the methods reached the step of preclinical trials.

IV. Conclusion

The performed analysis of organic nanoparticles and materials on their basis allowed certain conclusions and generalizations to be drawn. It deserves special mention that all the methods of producing organic nanoparticles cited in this review require further development and improvement. First of all, the problems of stabilizing organic nanoparticles, enhancing the efficiency of the methods of their fabrication and reducing their cost should be solved. In the industry, the only method used so far is the manufacturing of organic suspensions by mechanical grinding, which is utilized by many companies. The other methods analyzed in this review have not yet reached the industrial level. In the field of chemistry of organic nanoparticles, the studies are now aimed at accumulation of experimental data.

In this review, we have demonstrated that stable crystalline organic nanoparticles of various sizes and structures different from those of the original substances can be produced from solutions or the gas phase containing the original substances in the molecular state. We believe that the possibility of their formation largely depends on the size of the single crystals that appear in the liquid or gas phases under certain conditions. For organic nanoparticles, the size effect is of the structural-molecular nature and is manifested itself to the greatest extent in organic nanocrystals.

The following top-priority problems can be pointed out for studying and using organic nanoparticles:

— the extension of the range of organic compounds of different classes capable of serving as the precursors of nanoparticles;

— the elucidation of experimental criteria and widening of the methods of preparation of organic nanoparticles, the elucidation of the relationship between the chemical activity and the size of organic nanoparticles;

— the analysis of the size, shape and stability of nanoparticles, the trend to retain or change their properties, for example, spectral, in solutions, colloidal dispersions and in the crystalline state;

— the development of theoretical concepts on the size effect of organic nanoparticles on their spectral properties, based on the changes in the rigidity and elasticity of the crystal structures of organic compounds and the concomitant changes in the hierarchy of intermolecular interactions;

— the extension of the scope of application of organic nanoparticles in such fields as pharmaceutics, green chemistry, electronics, optoelectronics.

The solution of mentioned problems will favour the origination and the development of organic nanochemistry.

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