Nanoencapsulation of Antitumor and Antituberculosis Drug Preparations with Biocompatible Polymers

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Abstract: Controlled release of drugs at the locus of the targeted disease is one of the most challenging research areas in the pharmaceutical field. Nowadays novel drug delivery systems on the basis of polymers are attracting great attention since they can improve therapeutic efficiency of potent drug preparations decreasing the risk of side effects. By developing colloidal drug delivery systems such as liposomes/vesicles and polymeric nanoparticles and nanocapsules the pharmacokinetics of the drug can be changed and thus the therapeutic efficiency of the drug can be increased. Nanoparticles with their special characteristics such as small particle size, large surface area and high capacity of carrying biologically active substances offer a number of advantages compared to other colloidal drug delivery systems [1, 2].

Controlled drug release systems are constructed on the basis of natural and biocompatible synthetic polymers. Among the most promising biocompatible polymers human serum albumin (HSA), polyalkyl cyanoacrylates (PACA) and poly-D,L-lactic acid (PLA) are of great importance. Nanoparticles on their basis have been proven to be efficient in treatment of serious and long-termed diseases such as tumors, tuberculosis and bacterial infections [3-126]. Therefore this article is aimed to give a brief review on the research works devoted to the synthesis and investigation of polymeric nanoparticles and nanocapsules based on PACA, HSA and PLA for the past three decades.

Keywords: Drug delivery systems, nanoparticles, nanocapsules, polyalkyl cyanoacrylates, human serum albumin, poly-D,L-lactic acid.

1. INTRODUCTION

Nowadays the attention of the scientists of all over the world is concentrated on obtaining the materials with given properties which can be achieved by designing the objects in nano-level. Construction of the materials in nano-level allows to improve their properties significantly and/or to change them dramatically. It gives opportunity to take control over the object's or system's behavior changing its property by alteration of one of the parameters of the system.

Nanotechnologies or so called nanostructured materials with desired properties are involved in all branches of science and technology. They are of great significance in medicine and pharmacy. At present one of the top-priority tasks of modern pharmaceutical industry is the creation of drug with nearly "ideal" properties, i.e. the drug which can selectively affect on assigned place causing no damage on healthy organs and tissues and avoiding toxic effects of drug on organism in general. At present time about one forth of world sales volume of drugs occupy preparations with improved delivery properties. Among the widely used controlled drug release systems colloidal drug delivery systems such as polymeric nanoparticles and nanocapsules have gained special attention [1]. The number of investigations devoted to the preparation and use of colloidal drug delivery systems on the basis of polymers has grown tremendously within the past three decades [1-126]. When using polymeric nanoparticles and/or nanocapsules the efficiency of active substances was proved to increase considerably in comparison with free drugs [1-14].

The main idea of using colloidal drug delivery systems is based on three tasks: a) efficient encapsulation of the drug, b) targeted delivery of the drug to the organ or tissue of the body, and c) controlled release of the drug there. While circulating of polymeric nanocarriers in the organism biologically active substance contained in it is protected from inactivation, and the effect of drug is prolonged. Besides drug delivery systems on polymer basis offer following benefits: the possibility of incorporation of poorly-water soluble compounds, control of

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E-ISSN: 1929-5995/14

accumulation of the drug in different organs and tissues depending on particle size, considerable decrease of the amount of drug needed for treatment. Therefore the work out of drug formulations with sustained or controlled drug release on polymer basis is of current interest.

The task of creation of polymeric nanoparticles and nanocapsules is especially important in a treatment of diseases which require intensive and long-term therapy with high dosage of drugs. The problems of chemotherapy of tumor diseases and tuberculosis nowadays have taken global scale. The use of potent drugs for a long period of time often leads to expressed side reactions (toxic and allergic effects) thus considerably decreasing the treatment efficacy. Polymeric nanoparticles and nanocapsules are used in targeted drug delivery into the site of inflammation such as tumors and tuberculosis [1-28], therefore developing the novel forms of drugs for the delivery of antituberculosis (antiTB) and antitumor preparations on the basis of well-known biocompatible polymers would help to increase essentially the efficacy of chemotherapy of such diseases.

1.1. Nanoparticles and Nanocapsules as Colloidal Drug Delivery Systems

Nanoparticles for drug delivery were developed about 35 years ago. They were initially worked out as carriers for vaccines and drug preparations used in tumor chemotherapy. Nanoparticles by a definition given by Kreuter J. (which was later adopted by the Encyclopedia of Pharmaceutical Technology and the Encyclopedia of Nanotechnology) “are solid colloidal particles ranging in size from 10 to 1000 nm (1 μm). They consist of macromolecular material in which the active principle (drug or biologically active material) is dissolved, entrapped, encapsulated and/or to which the active principle is adsorbed or “attached” [1].

Generally, nanostructures can be divided into 2 groups. These are solid particles (matrix-type particles or monolithic devices) and hollow capsules – reservoirs as it’s shown in Figure **1**. Monolithic (matrix) devices are possibly the most common of the devices for controlling the release of drugs. This is possibly because they are relatively easy to fabricate, compared to reservoir devices.

The historical perspective of nanoparticles, i.e. the development of the concept of nanoparticulate systems can be found in the paper of Kreuter J. [8].

The development of controlled drug delivery systems based on polymeric nanoparticles and nanocapsules will be briefly reviewed in this article. The main focus will be on polymeric nanosystems of PACA, HSA and PLA.

A number of pharmaceutical investigations in the direction of the creation of systems for the controlled delivery of drug preparations using nanoparticles have been done in oncology [2]. Nowadays colloidal drug delivery systems such as micro- and nanoparticles, nanocapsules, liposomes and/or vesicles are created for controlled drug delivery [1]. Sub-micron size of the nanoparticles offers some specific advantages over microparticles and liposomes such as high colloidal stability in the organism and during storage [1, 13]. Nanocarriers were found to be accumulated in tumor tissues and in the inflamed tissues [11]; the particles of certain size are able to find the infected cells or tissues and act selectively without causing damage to the healthy tissues. Also small size of nanoparticles and nanocapsules allows them to penetrate through narrow blood capillaries [1]. It is shown that targeting specific organs is very sensitive for the submicron particle size and therefore narrow particle size distributions are advised [126].

High carrier capacity and ability to incorporate both hydrophilic and hydrophobic compounds make them attractive systems to be used in controlled drug delivery. Moreover, as it was reported by Desai *et al.*,

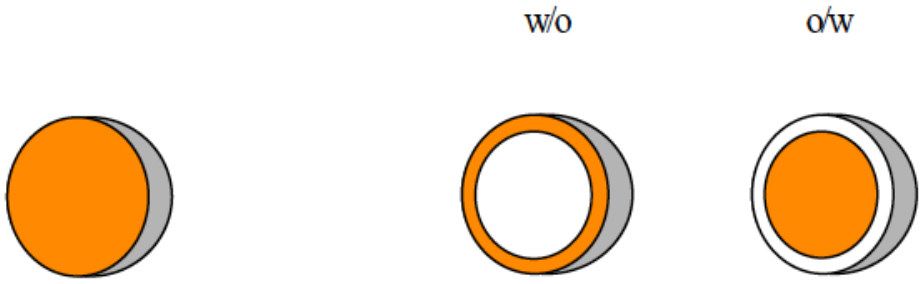

Figure 1: Nanosystems: solid micro- and nanoparticles and hollow capsules (w/o – water in oil and o/w – oil in water (inverse) systems).

nanoparticles have relatively higher intracellular uptake compared to microparticles [16]. They have demonstrated that 100 nm size nanoparticles showed 2.5 fold greater uptake compared to 1 μm microparticles and 6 fold higher uptake compared to 10 μm microparticles in the Caco-2 cell line [16]. Similar results were obtained when these formulations of nano- and microparticles were tested in a rat in a *in situ* intestinal loop model [17]. The efficiency of uptake of 100 nm size particles was 15–250 folds greater than larger size (1 and 10 μm) microparticles. Besides, a variety of routes of administration (intravenous, intramuscular, oral, inhalation, others) can be performed with sub-micron sized particles [13].

Apart from the size, the surface properties of the particles also play an important role when administering them into the body, as the size, particle size distribution and surface charge are responsible for the biodistribution of polymeric nanoparticles [11, 13, 54]. Therefore together with particle size and size distribution such parameter as the surface charge of the particles needs to be evaluated. In addition, better targeting can be accomplished by obtaining monodisperse systems (since the particles of determined sizes are accumulated in specific inflamated tissues) and/or by attaching antibodies or ligands on the surface of nanoparticles [41, 42]. In some cases the obtained polymeric nanoparticles are covered with surface modifiers such as polyethylene glycol (PEG) or polyethylene oxide (PEO) and other surfactants or high molecular weight polysaccharides (chitosan, dextran) to achieve specific surface properties [31]. The mechanism of biodistribution of the drug incorporated into the nanoparticles in the actual organism is a complex process. Its peculiarity consists in prolonged presence of the drug in blood plasma and further accumulation in different parts of tissues, as a rule, in liver and spleen [39-42].

1.1.1. Synthesis of Polymeric Nanoparticles and Nanocapsules

The method of preparation of polymeric nanoparticles and nanocapsules can be chosen depending on the goals, technological advantages, the properties of the substances entrapped and the polymeric materials to be used [1, 6, 13, 23, 27]. There are a number of methods for synthesizing nanoparticles: emulsion polymerization, emulsification-diffusion, interfacial deposition, desolvation, nanoprecipitation, solvent evaporation/extraction and solvent displacement methods [1, 6, 13, 23, 27].

One challenge is the production of these nanoparticles in the presence of the drugs, which in some cases requiring harsh synthesis conditions that are not suitable for sensitive compounds such as the drugs. Therefore for this kind of substances encapsulation with preformed polymer can be employed [127-129]. Nowadays there are various methods for the preparation of hollow structures for different purposes [81-97], such as layer-by-layer deposition using vesicles templating [82-86], the sacrificial core process in which the core is removed after formation of a thick and stable shell [82], interfacial polymerization or polycondensation in miniemulsions [82, 88-95].

In general there are some common rules in the different technological approaches for the preparation of nanoparticles and nanocapsules, however technological parameters have to be chosen for each system taking into consideration the nature of the biologically active substances in combination with the polymeric matrix [1, 6, 13, 23, 27, 82].

There are mainly two ways of performing the drug loading: 1) incorporation of the drug to the polymeric particles by dissolving it in the system (encapsulation); 2) adsorption of the drug on the nanoparticles. However when loading the drug by encapsulation method there is also possibility that some part of the drug can be adsorbed on the walls of the capsules as well. Nowadays both ways are used for obtaining drug-loaded polymeric nanoparticles.

Nanoparticles and nanocapsules that are synthesized with this purpose, based on natural and synthetic polymers, will be considered below.

Polymeric materials have wide application in medicine and pharmacy as implants, hydrogels, osmotic pumps, contact lenses, films filled with drugs, coatings of tablets, etc. If used in biomedical applications for the creation of nanosomal formulations, polymers need to meet several requirements:

- Biocompatibility;
- Rather high molecular weight to be able to circulate in blood stream for certain time;
- To be able to degrade in a biological medium to non-toxic products;
- Contain functional groups (-OH, -NH_2, -CHO, -COOH) needed for the creation of polymer-drug

conjugates (pendant-chain systems) and for surface modifications;

- Commercially available or the method of manufacture of the polymer is rather simple and cheap;
- Could be easily administered;
- Could be easily sterilized.

Nanosystems are constructed based on polymers which have a wide application in medicine. Specific requirements for the polymeric micro- and nanoparticles and nanocapsules restricted the number of polymers which can be used in drug delivery. In the early stages of drug delivery research only polymers on the basis of natural organic acids such as glycolic, lactic and malic acids were used. These polymers degrade in the organism to non-hazardous compounds. Also the biopolymers collagen, gelatin, bovine serum albumin and HSA, PLA, poly-glycolic acid and their copolymers (PLGA) have found application in medicine as drug carriers [1, 54, 58]. More recently nanoparticles and nanocapsules for biomedical purposes are synthesized based on polyvinylpyrrolidone, polylactic- and polyglycolic acids, poly-ε-caprolactone and PACA [1].

The binding of polymer with drug can be performed by attaching the drug to the polymer chain by covalent linkage or by weak bonds (Van der Waals, hydrogen bonds, dipole-dipole bonds, etc.). For the first time the model of a polymer bound drug system was suggested by H. Ringsdorf in 1975 (Figure **2**) [9, 100, 101].

According to the Ringsdorf model the polymeric carrier combines the elements of the system i.e. the solubilizing part (1) responsible for solubility of the drug bound to the polymer in the organism, the polymer-drug part (2) where drug is bound to the polymer chain by covalent linkage and the transporting part (3) which consists of the targeting molecules attached to the polymer chain [9, 100, 101]. In general, physicochemical properties of the polymer-drug complex contain the sum of the characteristics of these three parts. The main function of the polymer is to deliver the system into the targeted organ or tissue and release the drug there. The release mechanisms of biologically active substance from polymeric nanoparticles and nanocapsules will be considered further in 2.

1.1.2. Polymeric Nanoparticles for the Delivery of Antitumor and Antituberculosis Drugs

The results of numerous investigations have shown obvious potentials of the use of polymeric nanosystems for the treatment of such chronic diseases as tuberculosis, tumors, arterial hypertension and other diseases which demand long-term therapy with multiple doses of potent drugs [3-126].

Nowadays there are several research groups working basically on synthesizing polymeric nanoparticulate systems for controlled drug release. One of the founders in the field of creation of nanoparticles for controlled release purposes was prof. Peter Speiser (Eidgenössische Technische Hochschule Zürich) [8]. The most important ideas of prof. Speiser were the development of nanoparticles for targeted drug delivery and the idea of using nanoparticles for the delivery of drugs which have to pass through the blood–brain barrier and to be delivered directly to the brain [8]. Despite the doubts about the possibility of obtaining such systems for drug delivery, due to the efforts of the research group of prof. Speiser the idea was realized within less than 15 years [8]!

This direction was continued by the successor of prof. Speiser P. – prof. Kreuter J. (Institute of Pharmaceutical Technology, Goethe University, Frankfurt am Main, Germany). The research group under the supervision of prof. Kreuter for a long time has been working on developing polymeric systems for controlled release of antitumor drug doxorubicin, apoliprotein, DNA, RNA, etc. on the basis of different natural and synthetic polymers including HSA and

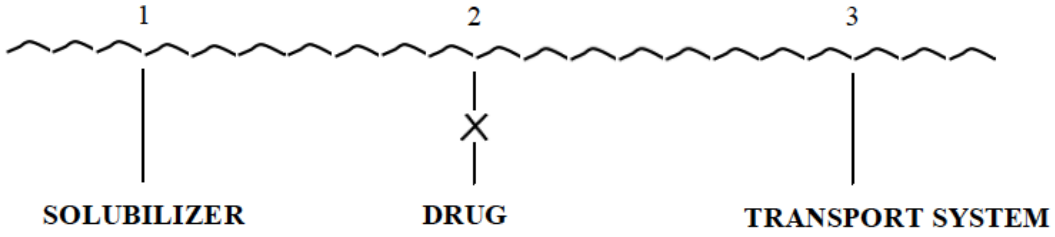

Figure 2: Ringsdorf model of synthetic polymer-drug conjugate.

PACA [1, 3, 4, 8, 35-37, 39-44, 50, 51, 59, 121, 122, 126].

Numerous investigations in the field of creation of nanoparticulate systems for antitumor drugs have been done by the research group of prof. Alyautdin R. (I.M. Sechenov *Moscow Medical Academy*, Center of Bionanotechnologies and Nanotoxicology, Russia) [45, 59]. In cooperation with prof. Kreuter J., prof. Gelperina S. (Moscow State University of Fine Chemical Technologies named after M.V. Lomonosov, Russia) is conducting research work in the direction of obtaining PACA nanoparticles for targeted delivery of antitumor and antiTB drugs [3, 4, 13, 14, 24-26, 43].

The group of prof. Couvreur P. (Université de Paris-Sud, France) over 30 years have been carrying out investigations on the synthesis of PACA nanoparticles loaded with drugs and have been studying their release profile [46-48, 52, 53, 56, 57, 62, 66, 74, 78, 79, 81, 99, 105, 106]. There is a start-up company in France (Bioalliance, Pharma) which produces PACA nanoparticles for clinical uses in phase III trials [47, 62, 79].

A number of antitumor drugs have been successfully encapsulated/incorporated into PLGA nanoparticles [111]. These are some specific examples: 9-Nitrocamptothecin was encapsulated in PLGA through the nanoprecipitation method, as a result the encapsulation efficiency was more than 30 % [111]. Paclitaxel-loaded nanoparticles were prepared by the solvent evaporation/extraction method; in this case the loading efficiency reached 100 % with full antitumor activity [112]. Cisplastin was encapsulated in PLGA-methoxy-PEG [113], the poorly water-soluble Xanthones was incorporated into PLGA nanoparticles [114]. Triptorelin-loaded PLGA nanoparticles have been synthesized by the double-emulsion solvent evaporation method; loading efficiency was found to vary between 4 % to 83 % [115]. Dexamethazone was incorporated into PLGA nanoparticles by the solvent evaporation method. The drug released completely after 4 h of incubation at 37^0C *in vitro*.

The antitumor drug Tamoxifen was incorporated into poly-ε-caprolactone nanoparticles surface modified with PEO by the solvent displacement method [116]. The authors claim that nearly up to 26% of the total activity of the drug could be applied in the tumor [116].

AntiTB drugs, being potent drugs, have various side effects which cause considerable toxic reactions of the organism when applied for prolonged time. Besides, most of the antiTB drugs have protein or peptide structures which are tend to degrade rapidly in biological fluids. Therefore the development of controlled release systems for these drugs is one of the important tasks of modern medicine. Numerous investigations have been done in this field with the aim of improving the therapeutic efficacy of antiTB drugs. The possibility of the creation of nanosomal formulations for rifampicin, isoniasid and pirazynamide in the form of an aerosol was studied by Gelperina S.E. [13, 14, 24]. In all three cases the content of drug loaded in the nanoparticles was more than 40 % of the applied amount during loading. The chemotherapeutic potential of these preparations when using them in aerosol formulations was investigated and rather high effectiveness of using such formulations in the treatment of tuberculosis mycobacterium was observed [24]. These authors also investigated the character of delivery of rifampicin, isoniasid, pirazynamide and ethambutol into the brain by nanoparticles obtained on the basis of copolymers of lactic and glycolic acid [24]. Considerable potential of using polymeric nanoparticles in comparison with standard preparations was claimed [24]. Johnson C.M. *et al*. studied the effectiveness of using antiTB drug preparations encapsulated in PLA nanoparticles in tuberculosis therapy [30].

Tsapis N. *et al*. [102] have synthesized large porous particles containing 95 % of what of antiTB drug p-aminosalicylic acid for direct delivery of the drug into the lungs *via* inhalation. It was observed that higher lung exposure to p-aminosalicylic acid can be reached at much lower drug levels in comparison with those necessary in oral dosage formulations when treating rats [102].

Characterization and Analysis of Nanoparticles and Nanocapsules

When synthesizing polymeric nanoparticles particle size and particle size distribution are the most important characteristics of nanoparticles as they determine the *in vivo* “fate” (biodistribution) of nanoparticles loaded with drug [1, 62, 79]. For that purpose commonly used methods such as dynamic light scattering (DLS) can be applied. This method can also give information about surface charge of the particles which is quantitatively characterized as zeta potential (using the Zetasizer): in acidic pH it has a positive charge, in basic pH – a negative charge. The zeta potential is an indicator of the stability of the colloidal system and the absence of excess counter ions is important because it may lead to aggregation;

the latter is not acceptable when using polymeric nanoparticles in drug delivery purposes. Transmission and scanning electron microscopes can be applied to evaluate the shape and surface of nanoparticles [47, 79].

Molecular weight is another important characteristic of the polymer as it influences the circulation time of nanoparticles in the body. Molecular weight and molecular mass distribution of the formed polymer can be analyzed by size exclusion chromatography (SEC) and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI TOF MS) [47, 79, 99].

Such techniques as FTIR- and ^{1}H NMR-spectroscopy, and thermal gravimetric analysis are usually used to confirm the incorporation of drugs into the polymeric matrix [15, 47, 79, 99].

For the determination of the binding degree of drug it's important to separate the nanoparticles from the serum. For this purpose ultracentrifugation or in some cases gel filtration can be successfully used. The concentration of unbound drug in supernatant can be measured using UV-Vis-spectroscopy or HPLC.

Estimation of the loading efficiency of the drug or loading capacity of the polymer can be performed using UV-Vis-spectroscopy as well as HPLC. These methods are also suitable to measure drug release rates from polymeric nanoparticles and nanocapsules. Drug release kinetics can be studied using ultracentrifugation or dialysis.

2. DRUG RELEASE AND DEGRADATION OF POLYMERS

Drug release has to be considered in conjuction with the degradation of polymers as the release of drug from polymeric nanoparticles is mainly governed by the degradation rate and degradation mechanism of the polymer. In this regard, biodegradability of polymeric carriers after performing the targeting function is a primary requirement for the chosen polymers [1, 100, 101]. The rate of polymer degradation should be optimal for the biomedical application. In general the drug-loaded polymer is first supposed to enter the cells and there it should undergo degradation [1, 100, 101].

In many cases the drug is not chemically bound to the polymer carrier and drug release occurs as a physical process: desorption of surface-bound drug and/or diffusion of the drug through the polymer. This diffusion process can be accelerated by the degradation of the polymer which in itself is enhanced by the presence of enzymes. Chemical degradation of polymer takes place if polymer has hydrolysable bonds and degrades to lower molecular weight compounds, finally forming CO_2 and H_2O. In many cases hydrolytic degradation goes together with enzymatic degradation in the organism. Therefore biodegradability of polymers is determined by the chemical structure of the polymers and their sensitivity to different enzymes [100, 101]. Polymers administered in the body can behave differently depending on their structure. Some polymers degrades to shorter chains within a day and eliminate through the kidney without any change, whereas others may circulate in the body longer and excrete from the organism gradually within weeks, months, sometimes years. In general, for safety reasons any xenobiotic has to leave the body within a certain period and it's not desirable that polymer remains in the organism several month or years as in many cases it may lead to pathologic processes [100, 101]. Some polymers undergo rather fast biodegradation and the formed fractions of lower molecular weight are easily eliminated from the body *via* kidney filtration.

Controlled biodegradation of polymers in some cases, allows to control the place and duration of the presence of biologically active substances [101]. For instance, synthesizing the polymer with known molecular weight and knowing the type of binding between "polymer-drug" one can judge about the duration within the drug is released [101]. The authors have shown that changing the structure of oligopeptides' sequences in the copolymers of N-(2-oxypropyl) methacrylamide it was possible to control the rate of cleavage of model drug from polymeric chain taking catepsin as an example [101]. Also studying the relation between molecular weight of polymer and the rate of permeation of poly-N-(2-oxypropyl) methacrylamide through the tissues of yolk bag it was found that the rate of accumulation of polymer in these tissues decreases considerably with the increase of molecular weight of the polymer [101].

Depending on the method of performing the loading, the drug release profile will be different: release of the drug adsorbed on the surface of nanoparticles will occur mainly as a result of desorption; the drug incorporated inside the polymeric matrix will most probably be released through diffusion, accelerated as a result of chemical degradation of the polymer.

Release kinetics of drugs from polymeric nanoparticles is determined by the type of the system.

Below examples of typical drug release profiles from polymeric nanoparticles and nanocapsules are described.

A) Drug Release from Polymeric Nanoparticles

- *diffusion-Controlled Systems*: matrix (monolithic) systems (solid micro- and nanoparticles) where the drug release occurs as a result of desorption of the surface-bound drug and/or diffusion of the drug from inner part of the particles;

- *chemically Controlled Systems*: a) biodegradable (bioerodable) systems. In this system drug releases as the polymer degrades; b) pendant chain systems (drug-polymer conjugates) are also considered as chemically-controlled systems since in this system the drug is covalently attached to polymeric chain and its release starts when the polymer-drug bond breaks down.

- *solvent Activated Systems:* Swelling controlled systems (nanoparticles) swell in a biological medium releasing the drug.

B) Drug Release from Micro- and Nanocapsules

Drug release profile from nanocapsules differs from the nanoparticles and depends on the properties of polymeric shell [11, 81-95]. Different types of polymeric shells can be used to perform controlled release:

- *diffusion-controlled devices* (with permeable shell) in which the release rate of drug from the system depends on the wall thickness and swellability, porosity, the pore size of polymeric shell, the concentration gradient of the drug, etc.;

- *responsive drug delivery systems*. These systems are sometimes called membrane-controlled reservoir devices. Drug release occurs by diffusion of the drug through a responsive shell (pH-, thermo-, ionic strength, magnetically- or ultrasonically-controlled). In these systems drug releases when an external trigger is applied and the diffusion rate through the shell is enhanced. They can be used in a treatment of diseases like diabetes where the dosage of drug is regulated and the drug is given when it's needed;

- *chemically-controlled devices* - the capsules with biodegradable shells, where the active substance' release is a consequence of polymer degradation in a biological medium;

- *osmotically-controlled delivery devices* which mainly have a semi-permeable shell that allows to move water into the capsule and the drug will only come out when there is an osmotic pressure. The two-compartment osmotic pump is one of the varieties of this type of capsules.

3. POLYALKYL CYANOACRYLATE BASED CONTROLLED DRUG DELIVERY SYSTEMS

Among synthetic polymers which have found wide application in the biomedical field PACA are of special interest. Due to the high reactivity and ability to create strong bonds alkyl cyanoacrylates have been successfully used for about 60 years in medicine as surgical sutures, stitches and adhesives for wound closure [1, 4, 15, 18-21, 26, 46-57, 59, 60, 62-72, 74-76, 78-81, 99, 105, 106]. The ability of alkyl cyanoacrylates to firmly stick two pieces together is based on their high sensibility to OH-ions starting the polymerization rapidly. Nowadays mainly 2 types of surgical sutures n-butyl cyanoacrylate (Indermil, liquiband) and octylcyanoacrylate (Dermabond) are used clinically in European countries, in Canada and in the USA [79, 99].

Polymers on the basis of alkyl cyanoacrylates are known to be biocompatible and biodegradable. Owing to these properties PACA are unique materials for the creation of polymeric carriers of drug preparations in the formulations of nanoparticles and nanocapsules [46-48, 52, 53, 56, 57, 62, 66, 74, 78, 79, 81, 99]. PACA were first introduced as drug delivery systems in the formulations of colloidal nanoparticles in early 80s of 20^{th} century [78, 79, 81]. Later PACA nanoparticles were used for the transport of rapidly-degrading substances such as proteins and nucleic acids [79]. Since that time PACA continue to attract attention of researchers in the pharmaceutical field as drug delivery systems. The potential of PACA as carriers for different drugs has been shown by numerous investigations [1, 8, 11, 47, 48, 62].

Mainly two kinds of techniques are used for the manufacture of PACA nanoparticles and nanocapsules; these are conventional emulsion polymerization (leading to nanoparticles) and interfacial polymerization (leading to nanocapsules) respectively. The main difference between the nanostructures obtained by these methods is the release profile of drug, which is

first-order when using nanoparticles and zero-order for nanocapsules [11, 47, 48, 54].

More detailed reviews on the synthesis, characterization, methods of investigations and *in vitro* and *in vivo* toxicity of PACA nanoparticles and nanocapsules can be found in [1, 8, 11, 47, 48, 62].

3.1. Polyalkyl Cyanoacrylate Nanoparticles for the Transport of Drugs

Synthesis of PACA Nanoparticles by Emulsion Polymerization

The emulsion polymerization method for alkyl cyanoacrylates was first introduced by Couvreur P. in 1979 with the aim of obtaining polymeric nanoparticles for targeted drug delivery [81]. The first studies of Couvreur P. *et al.* were devoted to the investigation of the toxicity of PACA nanoparticles and developing nanosomal formulations for antitumor drugs [78, 79, 81].

One of the main advantages of PACA in comparison to other synthetic carriers is the simplicity of carrying out the polymerization process. There are three routes of polymerization for alkyl cyanoacrylates - radicalic, anionic and zwitterionic mechanisms [46-48, 52, 53, 56, 57, 62, 66, 74, 78, 79, 81, 99]. Polymerization of alkyl cyanoacrylate by a free radical mechanism requires higher temperature and conditions which suppress polymerization of monomer by the two other routes, for instance, absence of the traces of weak bases including water which may catalyze ionic polymerizations. By carrying out the process by the free radical mechanism one can obtain product with higher molecular weight (higher than 3000 Da) and a higher glass transition temperature (T_g) [79, 99]. However, due to less harsh polymerization conditions and simplicity of carrying out the process, polymerization of alkyl cyanoacrylates by anionic routes is in many cases more preferable [47, 79, 99]. In contrast to other polymerization systems the polymerization of alkyl cyanoacrylates in water by this route doesn't require special conditions to start the reaction [47, 79, 99]. Polymerization of alkyl cyanoacrylates by anionic route is rapidly initiated in the presence of weak bases (Lewis bases), including water at room temperature. The reaction is terminated by protons. The rate of polymerization of alkyl cyanoacrylates by the anionic route strongly depends on the pH of the medium: the higher the pH the faster the reaction, so in a basic medium polymerization finishes within a few seconds, the reaction is not controllable and leads to coagulation, whereas sustaining acidic pH gives opportunity to synthesize stable particles of nanometer size. As a consequence of the high termination rate the molecular weights of the formed polymers in many cases are in the range of 600-3000 Da [1, 78, 79, 81].

Factors Affecting Physicochemical Characteristics of the Nanoparticles

System parameters such as type and concentration of surfactant, temperature, monomer content, pH of the medium and stirring rate have a considerable influence on the characteristics of the produced PACA nanoparticles [1, 47, 79, 99]. The most important factors are the pH of the medium and the concentration of monomer and surfactant [1]. It was shown that stable PACA nanoparticles of different sizes can be obtained at a monomer concentration varying from 0.05 to 7 % and the pH of the medium not exceeding 3.5 [1].

Loading Efficiency

There are mainly two ways of performing drug loading: 1) incorporation of the drug into the system before the reaction has started; 2) introduction of the drug after termination of the reaction or after some time when initiation took place (partly adsorption) [1, 47, 79, 99]. Obviously the loading efficiency of the drug into the polymeric matrix is determined by the time of introduction of the drug into the reaction medium. A high binding degree can be achieved by dissolving the drug in the aqueous medium before adding the monomer into the system [15, 18-24, 72].

Reddy Harivardhan L. *et al*. synthesized nanoparticles of polybutyl cyanoacrylate (PBCA) loaded with methotrexate by emulsion polymerization and dispersion polymerization techniques by anionic polymerization [69]. The drug was dissolved in the polymerization medium prior to addition of butyl cyanoacrylate [69]. Properties of the obtained polymeric particles and release kinetics of the drug were compared [69]. The influence of monomer concentration on entrapment efficacy and particle size of PBCA nanoparticles loaded with drug obtained by the two methods was considered [69]. The entrapment efficiency is found to increase with increasing the monomer concentration in the system. No appreciable change in particle size of the nanoparticles synthesized by emulsion polymerization has been noticed when using monomer concentrations in the range of 1-3 % [69].

Daunorubicin was successfully incorporated into PBCA nanoparticles by carrying out polymerization in the presence of the drug with entrapment efficiency up to 100 % [15]. However, the use of daunorubicin-loaded PBCA nanoparticles didn't improve to a great extends the effectiveness of the drug toward the resistant cells compared to free daunorubicin [15].

Polyethylbutyl cyanoacrylate nanoparticles loaded with ciprofloxacin were synthesized by Page-Clisson M.-E. *et al.* by adding the drug prior to polymerization [22]. However the authors reported that prevention of aggregation of the drug-loaded nanoparticles was only possible when acetone was present in the initial reaction mixture for emulsion polymerization [22]. Drug release from synthesized nanoparticles was investigated in the presence of esterase and found to be very slow: about 50 % of ciprofloxacin released within two days [22].

Drugs of basic nature can initiate the polymerization reaction of alkyl cyanoacrylate, leading to covalent binding of the drug with the polymer, which of course can influence the biological activity of the drug. It has been reported that after addition of insulin (which has numerous amino-groups in its structure) in acidified aqueous solution prior to the start of the polymerization, PBCA particles of nanometer size were not formed, but when introducing the drug into dispersion right after the initiation stage, monodisperse polymeric nanoparticles have been obtained [18].

Phenyl butazone, which has nucleophilic nature, could act as an initiator and reacted with the monomer – isobutyl cyanoacrylate [67]. In case of the introduction of vidarabine and somatorelin (GRF) in a PACA matrix the initiation of the reaction by these drugs was observed as well [67].

There are some examples of addition of drugs at different times during the reaction [4, 5, 17, 19]. So this way the drugs can successfully be incorporated into polymeric matrix and/or adsorbed on its surface.

Generally, emulsion polymerization of alkyl cyanoacrylates by the anionic mechanism is known to be more suitable for the loading of water-soluble drugs, although it was reported that the incorporation of hydrophobic drugs into a PACA matrix was also possible by addition of cyclodextrin into the polymerization medium as it helps to increase the drug's solubility in the reaction medium [47, 79, 99].

When creating polymeric carriers for targeted drug delivery such alkyl cyanoacrylates as ethyl-, butyl-, isobutyl-, hexyl-, isohexyl- and octyl cyanoacrylates are the most effective ones as the resulting polymers have satisfactory characteristics and show a good biodistribution [15, 18-24, 72, 79, 99]. Also copolymers of ethyl- and butyl cyanoacrylates and butyl- and octyl cyanoacrylates are used (including core-shell structures) for the transport of drugs [61, 63].

It is shown that the surface modification of PACA nanoparticles using surfactants like PEG, polysorbates, poloxamers and others improves physicochemical parameters and biodistribution of nanoparticles [1, 4, 59]. Alyautdin R. *et al*. have investigated the possibility of using PBCA nanoparticles for targeted delivery of tubocurarine into the brain [59]. They have reported that PBCA covered with polysorbate-80 allows the quaternary amine of tubocurarine to penetrate through the blood brain barrier, which is not possible when using the standard form of the preparation [59].

Successful association of the antisense oligonucleotides with polyisobutyl- and polyisohexyl nanoparticles by adsorption using different surfactants was reported [46]. The protection of the oligonucleotides from hydrolysis by enzymes was possible when they were complexed with cetyltrimethyl ammonium bromide [46].

In some cases short co- and terpolymers of alkyl cyanoacrylates are obtained using the polymers which serve as surfactants (e.g. PEG, PEO, etc.) [31, 33].

PACA Nanoparticles in Treatment of Tumors

Nanoparticles of determined sizes are known to be able to reach tumor cells and to act selectively without causing damage to healthy tissue, as they only attach to the inflamed tissues. Also PACA was found to enhance *in vivo* activity of some antitumor drugs and antibiotics [46].

Over the last three decades investigations on the synthesis of nanocarriers based on natural and synthetic polymers are carried out in the laboratory of prof. J. Kreuter (Institute of pharmaceutical Technology of Goethe University, Germany). Most attention of the scientists at the Goethe University is given to medicines effective against brain tumors [1, 3, 4]. Under the supervision of prof. Kreuter, jointly with the research group of Gelperina S.E. (Moscow State University of Fine Chemical Technologies named after M.V. Lomonosov, Russia) it was found for the first time that PBCA nanoparticles covered with Polysorbate 80 can cross the blood-brain barrier [3, 4], whereas the

active substance itself was not able to penetrate to the brain.

There are a number of examples of incorporation of different cytostatic drugs (doxorubicin hydrochloride, actinomycin D, daunorubicin and others) and antibiotics (amikacin, ampicillin, ciprofloxacin, etc.) into a PACA nanoparticles' matrix with the aim of increasing the therapeutic effect of the drug [5, 12, 14, 15, 18-26]. Loading of hydrophilic formulations of drugs (ampicillin, doxorubicin hydrochloride, actinomycin D) to the polymeric matrices gives opportunity to achieve rather high binding degree [3-5, 72]. The antitumor drug ftorarur was successfully loaded into polyethyl cyanoacrylate (PECA) and PBCA nanoparticles by adsorption of the drug onto pre-prepared particles or incorporation of ftorarur during the polymerization process [63]. The route *via* adsorption afterwards led to rapid *in vitro* release of the drug from the nanoparticles [63], however loading of the drug by incorporating it during the process of the particle formation achieved higher loadings and a slower release [63]. Drug formulations of the combinations of PACA nanoparticles with ampicillin, amikacin and gentamicin were described [21, 72, 130].

The attempts to bind novel antitumor drug Arglabin created by Kazakhstani scientists into PBCA nanoparticles have been done by prof. Burkeev M.Zh. *et al.* [131]. PBCA nanoparticles loaded with antitumor drug Argalbin with satisfactory physicochemical characteristics and high binding degree (up to 70 %) have been successfully synthesized [131].

PACA Nanoparticles in Treatment of Tuberculosis

The treatment of such a disease as tuberculosis requires extensive chemotherapy using huge amounts of drugs for a long period which is first of all very toxic for human, inconvenient and extremely expensive. In this regard, Gelperina S.E. with coworkers investigated the possibility of incorporation of first-line antiTB drugs – isoniasid, rifampicin and streptomycin into polybutyl- and polyisobutylcyanoacrylate (PIBCA) nanoparticles [24]. They developed nanosomal formulations for the antiTB drug rifampicin on the basis of PBCA and have studied the influence of its composition on the biodistribution of the drug [24]. These authors also have synthesized PBCA nanoparticles loaded with the antiTB drugs streptomycin and moksifloxacin and they have investigated the release kinetics of the drugs [24, 26]. It was shown that after 2 days about 26 % of the moksifloxacin still remained in the particles [26]. Increase of therapeutic efficiency was observed when using nanosomal formulations of these drugs in treatment of acute bacterial infections in comparison with standard drug formulations [7, 24-26].

PECA nanoparticles loaded with antiTB drug capreomycin sulfate have been obtained by the research group of prof. Burkeev M.Zh. together with prof. Van Herk A.M. [132]. It was possible to achieve narrow particle size distributions for PECA nanoparticles loaded with the drug. It has been established that PECA both with and without drug will not accumulate in the human body being rapidly degradable (number molecular weights of PECA were around 2000). The results of the drug release study

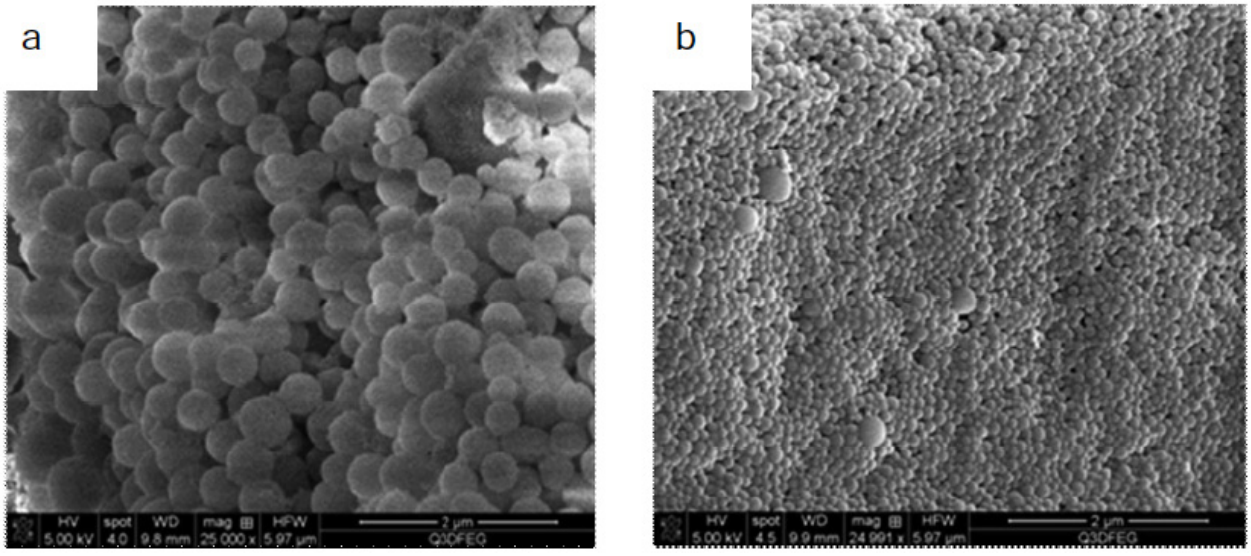

Figure 3: PECA nanoparticles loaded with antiTB drug capreomycin sulfate obtained by incorporation of the drug before (**a**) and 30 min after (**b**) the start of the polymerization reaction.

have shown the possibility of controlling the release rate of capreomycin sulfate by incorporation of this drug into PECA nanoparticles [132]. On the basis of the results obtained it was concluded that PECA nanoparticles would be a potential system to use them in tuberculosis treatment as carriers for the delivery of the antiTB drug capreomycin sulfate. The images of drug-loaded PECA nanoparticles are shown in Figure **3** [132].

3.2. Nanocapsules Prepared from Polyalkyl Cyanoacrylates for Targeted Drug Delivery

The importance and potential of the use of PACA in drug delivery research as polymeric nanocapsules have already been proven by the results of numerous investigations [81-97, 133, 134]. Drugs or other substances (dyes, inks, cosmetics, and so on) can easily be encapsulated in PACA nanocapsules as they can form reservoirs with a good morphology (stable and hard wall). Water-containing nanocapsules were found to be very suitable systems for the encapsulation of proteins, peptides and short fragments of nucleic acids [83, 88, 91, 95]. PACA nanocapsules can be obtained by polymerization of alkyl cyanoacrylate in water in oil (w/o) interfacial miniemulsion polymerization. The method of interfacial polymerization in microemulsion was for the first time introduced by Gasco and Trotta and used for preparation of PACA nanocapsules more than 20 years ago [89]. Hollow polyisohexyl cyanoacrylate nanocapsules containing an oil core have been synthesized by Chouinard F. *et al*. using this method [133]. The effect of the components of the system and process parameters on the nanocapsules' size has been explored [133]. The monomer concentration was found to play a major role in controlling the particle size, whereas pH of the medium led to slight change of the size of nanocapsules [81-88]. Further these authors have synthesized similar system using PIBCA [134].

The influence of the time of addition of the model compound to the polymerization medium on efficacy of incorporation of the substance into the capsules was studied by Grangier *et al*. [104]. These authors have found that for a hormone-releasing factor its addition into the reaction medium 15-30 minutes after the start of the polymerization is the optimal time, however when using isobutyl cyanoacrylate as a monomer this time has to be increased up to 5 hours [104]. Also it was shown that by addition of the substance shortly after the start of the polymerization a high degree of encapsulation can be achieved (90 %) [104], although in this case part of the drug can be lost at the beginning of the reaction acting as initiator.

Interesting results were obtained by M. Fresta *et al*. [92] when encapsulating antiepileptic drugs in oil-core suspensions using the method of Khoury Fallouh *et al*. with some modifications [97]. The mixture of Miglyol 812 with different organic solvents (ethanol, acetone, acetonitrile) was used as an organic phase [92]. Three antiepileptic drugs (Ethosuximide, 5.5-diphenyl hydantoin and carbamazepine) were encapsulated with loading efficiency 1-11 % [92]. The authors have revealed that the presence of ethanol leads to the formation of solid nanoparticles with diameters in the range of 100-400 nm as well as nanocapsules [92]. It was shown that encapsulation of these drugs in PECA nanocapsules enabled decrease of the *in vitro* release rate of carbamazepine [92]. It's worth noting that in all drug-nanocapsule systems an initial burst release to the medium was observed [92]. This behavior is explained by authors by the release of small amount of the drugs which were attached to the outer surface of the capsules [92].

Later antisense oligonucleotides have been encapsulated in PIBCA nanocapsules with the aim of protection them from enzymatic degradation [106]. The protection from degradation by nucleases of oligonucleotides was achieved by incorporation into nanospheres or by encapsulation inside nanocapsules. It was concluded that efficient protection was obtained when oligonucleotides are encapsulated rather than adsorbed on nanospheres [106]. Miyzaki Sh. *et al*. succeeded in obtaining PBCA nanocapsules loaded with indometacin and incorporating them into a gel composition thus improving transdermal delivery of the drug [91]. Similar to Lambert G. *et al*. these authors claimed that nanoencapsulation was more effective to protect oligonucleotides from degradation in biological fluids rather than entrapping or adsorbing them on solid nanoparticles [91]. A few years later Hillaireau H. *et al*. have found that encapsulation of mono- and oligo-nucleotides is only possible in the presence of water-soluble polymers [106]. The authors reported that the presence of cationic polymers (poly(ethyleneimine), chitozan) in nanocapsules made of PIBCA enabled successful encapsulation. Using PACA without water-soluble polymers caused leakage of mono- and oligonucleotides from the nanocapsules [106]. The results of an *in vitro* study of drug release from these systems have shown that only a limited initial burst-effect was noticed and zero-order release for 12 h was observed [106].

Another method of encapsulation by polymerization in a w/o interface has been proposed by Watnasirinchaikul *et al.* This method consists of dissolving the monomer in an organic phase followed by dispersing it in a water phase containing the drug [90]. Nanocapsules of PECA filled with insulin with loading efficiency of up to 80 % were obtained in this way [90]. Liang M. *et al*. have investigated the possibility of increasing the entrapment of peptides by functionalizing them and copolymerizing with alkyl cyacnoacrylates in w/o microemulsions using the method proposed by Hillery *et al.* and Watnasirichaikul *et al*. [107]. Encapsulation efficiency of functionalized peptides was found to increase with increasing the amount of monomer used for the polymerization [107]. Release profile of peptides from PACA nanoparticles and PACA nanocapsules has been compared [107]. It was observed that 50 % of the peptide releases within 10 min when using nanoparticles, confirming the burst release and 90 % of total drug was detected in solution after 6 h (measured at pH 8). From the nanocapsules only 10 % of total amount of the peptide was observed in the medium after 10 min, but the concentration of peptide didn't change in the medium within the whole period of observation [107]. This is the confirmation that copolymerization reaction between functionalized peptide and alkyl cyanoacrylate monomer took place; therefore the rest of the peptide was covalently bound to the polymer chain and was not released [107].

The efficacy of encapsulation of different water-soluble substances into PACA nanocapsules depends on molecular weight of the substance which is captured inside of the shell [95]. It was revealed by Pitaksuteepong T. *et al*. that with the increasing the molecular weight of the substance which is being encapsulated the efficacy of incorporation increases: when obtaining nanocapsules loaded with model compound fluorescein isothiocyanate conjugated dextran 10 the efficacy of encapsulation was 55 %, whereas using fluorescein isothiocyanate conjugated dextran 70 resulted in an increase of extent of encapsulation up to 90 % [95].

The functionalization of the surface of PBCA with amines and amino acids was done by Clemens K. *et al*. with the aim of obtaining stable nanocapsules with desired surface properties which could further be used to attach antibodies for targeting purposes [108]. The authors considered the influence of surfactant concentration, sonication time, pH, concentration and amount of initiator on particle size and size distribution of polymeric nanocapsules [108].

Recently Musyanovich A. and Landfester K. [88] have shown that by using polymerization of alkylcyanoacrylates in the w/o interface it is possible to obtain stable and compact nanocapsules. So using a modified technique, the authors [88] have synthesized PBCA nanocapsules containing DNA molecules and they have investigated the effect of pH, monomer concentration, the nature of surfactant and medium on physicochemical characteristics (thickness of shell, size of capsules, morphology, molecular weight and efficiency of encapsulation) of nanocapsules. The examples of successful formation of nanocapsules by

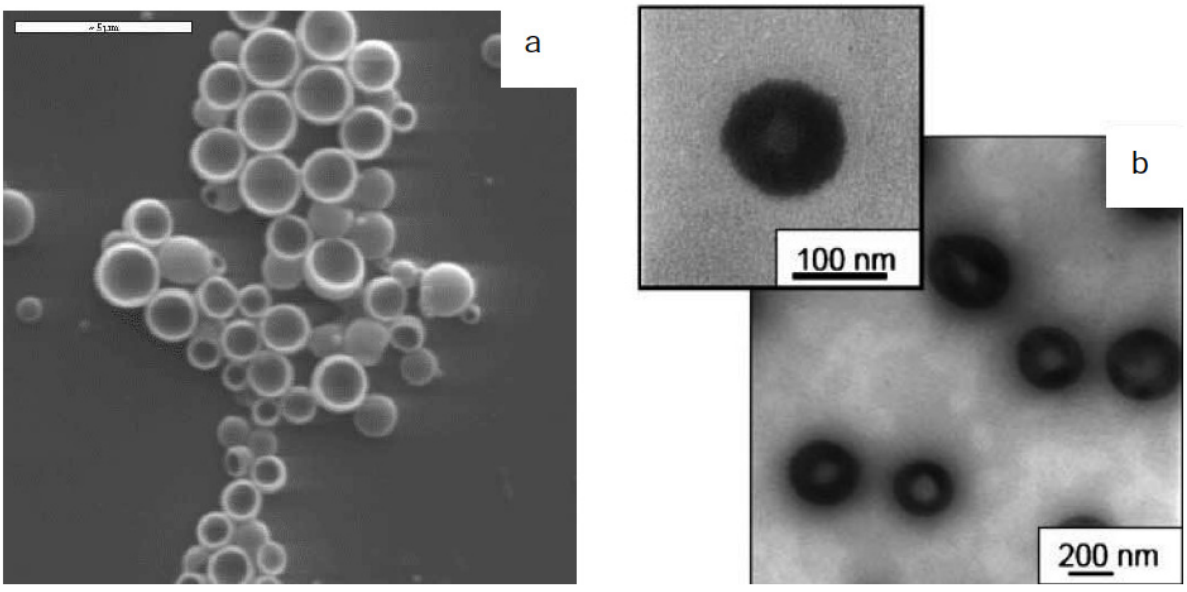

Figure 4: Images of nanocapsules prepared by miniemulsion polymerization: **a**) SEM; **b**) TEM [88].

interfacial polymerization in miniemulsion are presented in Figure **4** [88].

Characterization and Analysis of PACA Nanoparticles and Nanocapsules

Unlike other commonly used monomer's polymerization kinetics the observation of the polymerization kinetics of alkyl cyanoacrylates is difficult due to extremely fast polymerization rate [99]. For polymerization of alkyl cyanoacrylates in solvents micro-RAMAN-spectroscopy and dilatometry for *in situ* determination of reaction rate were suggested by Vauthier *et al*. [47, 79, 99].

The amount of alcohol eliminated to the medium as a result of chemical degradation of PACA can be detected by UV-Vis-spectroscopy, HPLC or gas chromatography [99].

3.3. Drug Release and Degradation of Polyalkyl Cyanoacrylate Nanosystems

The main difference between the nanostructures obtained by conventional emulsion polymerization and interfacial polymerization of alkyl cyanoacrylates is the drug release profile, which is first-order when using nanoparticles and zeroth-order for the nanocapsules [80, 135]. However, as it was shown above, in some cases burst release of the drug from PACA nanocapsules can be observed as well, which is the result of the release of drug bound to the walls of the nanocapsules [107].

Drug release from PACA nanoparticles and nanocapsules has been shown to be a consequence of polymer degradation and it is strongly dependent on the monomer and drug to be used and the preparation method applied to synthesize drug-loaded polymeric nanoparticles and nanocapsules [1, 79, 99]. Drug release usually will take place in parallel with chemical degradation of the polymer. The release of the human growth hormone from PIBCA nanospheres was found to occur in parallel with the degradation of the nanospheres [104].

In general, the degradation rate of PACA is in linear dependence on the side chain length: the longer the chain the longer the degradation time [46-48, 78, 79, 99]. PACA has two routes of chemical degradation in biological media: 1) degradation of polymer with the formation of formaldehyde; 2) hydrolysis of ester group with the formation of alcohol and polyalkyl cyanoacrylic acid (Figure **5**) [1, 78, 79]. Degradation of PACA is believed to go mainly by the second pathway [1, 78, 79, 99]. It was shown by several authors [99] that in strong basic medium (at pH 12) 85% of the total expected amount of iso-butanol was found in a solution after degradation of PIBCA nanoparticles, whereas the concentration of formaldehyde was only 7% [80, 99, 135]. Besides, this degradation pathway is catalyzed by various esterases which are present in organism [135] and is considered to occur as the major degradation pathway *in vivo* [79, 99].

There is one more mechanism suggested by Ryan and McCann [135], according to which the degradation starts by base and consists of an unzipping depolymerization of the parent polymer with immediate repolymerization to produce a new polymer with a lower molecular weight. However due to very fast degradation rate (within few seconds) it was not possible to detect it so far [99, 135].

4. HUMAN SERUM ALBUMIN AS A POLYMER CARRIER FOR CONTROLLED DRUG DELIVERY

HSA is one of the most frequently used biopolymers in medicine. HSA is known to be used for treating shock, burns, hypoalbuminemia, after surgery trauma, cardiopulmonary bypass, acute respiratory distress and hemodialysis [110]. Albumin-conjugates are also used in treatment of arthritic diseases, for liver targeting, and

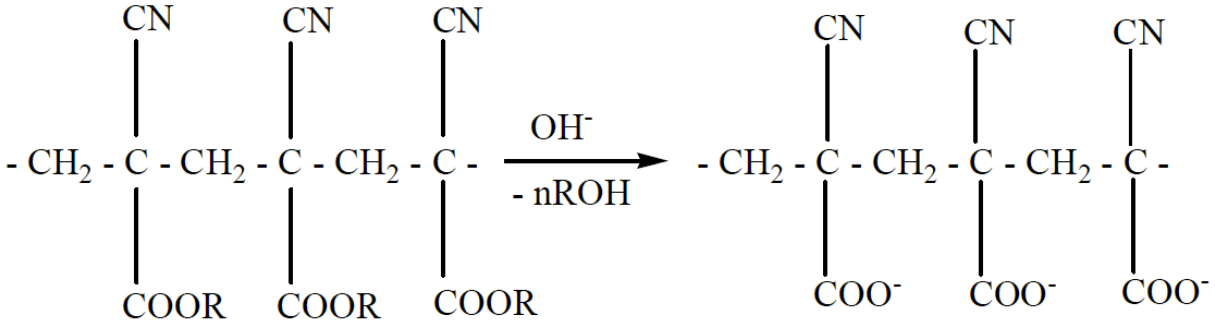

Figure 5: Degradation of polyalkyl cyanoacrylates by hydrolysis of ester group.

others [110]. Albumin is known to be accumulated in malignant and inflamed tissues [110]. Nanoparticles made of HSA were found to be non-toxic and well-tolerated by human organism [39-41, 111-113]. Owing to its capability to transport low molecular weight compounds it is a unique carrier for drugs. Binding drugs with albumin provided prolonged effect of such proteins and peptides as Albuferon and Levemir [110]. Functional groups (carboxylic and amine groups) which are present in the structure of albumin allow to modify the surface of the particles by attaching the molecules for targeting purposes [117-124]. For these reasons HSA is a potential drug carrier.

Nanoparticulate systems on the basis of albumin obtained by the desolvation method were first developed by R. Oppenheim and J. Marty in the 1970s [119, 120]. Since that time various active agents (methotrexate [110, 112], doxorubicin [1, 110], paclitaxel [110], antisense oligonucleotides [40], apolipoprotein AI and apolipoprotein B-100 [43], obidoxime [121, 122], noscapine [123]) have been successfully coupled to HSA nanoparticles. Some of these albumin-drug conjugates (methotrexate-albumin conjugate, albumin-based prodrug of doxorubicin, paclitaxel loaded HSA nanoparticles (Abraxane)) have passed clinical trials [110]. Abraxane was approved for treating metastatic breast cancer [110].

A detailed review on albumin-based prodrugs and the state-of-the-art of drug-loaded HSA nanoparticles can be found in [1, 110].

Some examples of drugs bound to HSA nanoparticles and their characteristics will be briefly reviewed below.

Over the last 20 years the research group under the supervision of prof. Kreuter J. is working on the synthesis of HSA nanoparticles loaded with drugs and the investigation of their efficiency applied to animals. Numerous studies have been performed to obtain HSA nanoparticles bound with a variety of cytostatics and to explore their *in vitro* and *in vivo* toxicity as well as their biodistribution and therapeutic efficacy in treating diseases [1, 35-37, 39-44].

Synthesis of HSA Nanoparticles

Generally nanoparticles of HSA can be synthesized by protein denaturation in w/o emulsion and applying desolvation (coacervation) methods as shown in [1, 35-37, 39-44, 110]. When obtaining albumin nanoparticles by desolvation, HSA is dissolved in water and then desolvated with ethanol and stabilized by addition of a cross-linker [1, 35-37, 39-44]. Particle size of the obtained nanoparticles usually varies between 80-300 nm.

Sebak S. *et al.* have synthesized HSA nanoparticles for the transport of noscapine with a size range of 150-300 nm and a loading efficiency of at least 85 % [123]. *In vitro* release studies have shown slow release profiles for different concentrations of the drug: at minimum concentration (5 mg/ml) of noscapine only 15 % of the whole amount of drug released after 24 hours and when using the highest concentration (15 mg/ml) around 20 % of loaded drug released within the same period of time [123].

HSA nanoparticles conjugated with cytostatic methotrexate have been obtained by Taheri A. *et al*. [124]. When testing the effectiveness of these nanoparticles, increased cytotoxicity of drug-conjugated nanoparticles on T47D cells compared to the free drug has been observed [124].

Factors Affecting Physicochemical Characteristics of HSA Nanoparticles

The most crucial factors influencing the stability of the system are the pH of the medium and the rate of addition of the desolvating agent [36, 122, 123]. The pH value influences the surface charge of the particles, in an acidic medium the zeta potential is positive and changes to negative in a basic solution. The HSA desolvation system becomes unstable at the isoelectric point [pI] of the HSA nanoparticles, i. e. 5.05. Therefore an alkaline pH combined with ethanol addition rates between 0.5 and 2.0 ml/min were recommended for desolvation [122]. The stability of HSA nanoparticles is also affected by the amount of the crosslinking agent added to the system [35, 36].

Loading Efficiency

Similar to other polymeric systems, the loading of the drug can be performed by adsorption of the drug onto preliminary prepared empty HSA nanoparticles or incorporation of the drug by dissolving it in the system during the crosslinking process [1]. Doxorubicin-loaded HSA nanoparticles have been successfully synthesized by the same research group [37] using the desolvation method. Loading of the drug has been carried out by adsorption of doxorubicin onto nanoparticles and incorporation of the drug by dissolving it in the solution followed by crosslinking of the particles with glutaraldehyde [37]. Both processes resulted in a high

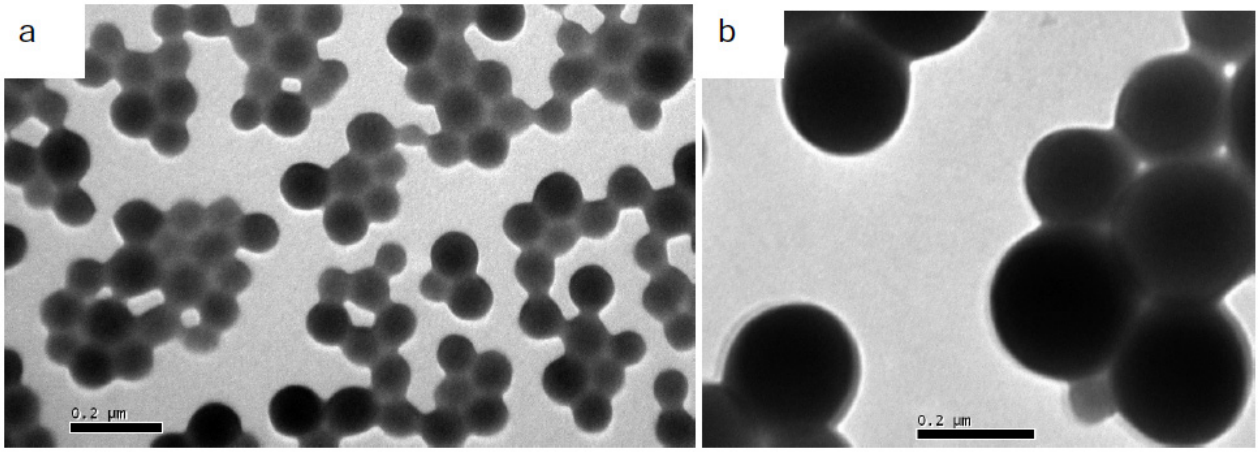

Figure 6: HSA nanoparticles loaded with antitumor drug arglabin by adsorption (**a**) and incorporation (**b**) methods.

binding degree of the drug with HSA as well as high stability of nanoparticles over more than 6 months [37]. It is important to note that an increase of the antitumor effect of the drug was noticed in comparison with the pure drug solution [37].

Kufleitner J. *et al*. performed [121, 122] the binding of obidoxime to HSA nanoparticles, both by adsorption of the drug on the surface of the synthesized particles and by incorporation in the interior of the particles. It is shown that when adsorbing the drug on HSA nanoparticles, the particles with a mean size of 268 nm have been obtained and around 60 % of drug was loaded by this method [121, 122].

Jointly with research group of the Institute of Pharmaceutical Technology of Goethe University by the scientists of Kazakhstan under the leadership of prof. Burkeev M.Zh. HSA nanoparticles loaded with antitumor drug Arglabin and antiTB drug p-amino salicylic acid (PASA) have been synthesized by the desolvation method [136, 137]. Both forms of antitumor drug Arglabin – hydrophobic native (substance) arglabin and dimethylaminoarglabin hydrochloride have been used for immobilization into the matrix of HSA. The loading of the drugs has been performed by two ways: 1) adsorption of the drugs onto the surface of preliminary prepared empty nanoparticles; 2) incorporation of the drugs to the polymeric particles by adding them into the system during crosslinking of albumin macromolecules (Figure **6**).

The nanoparticles based on HSA loaded with the antitumor drug Arglabin and antiTB drug PASA allowed

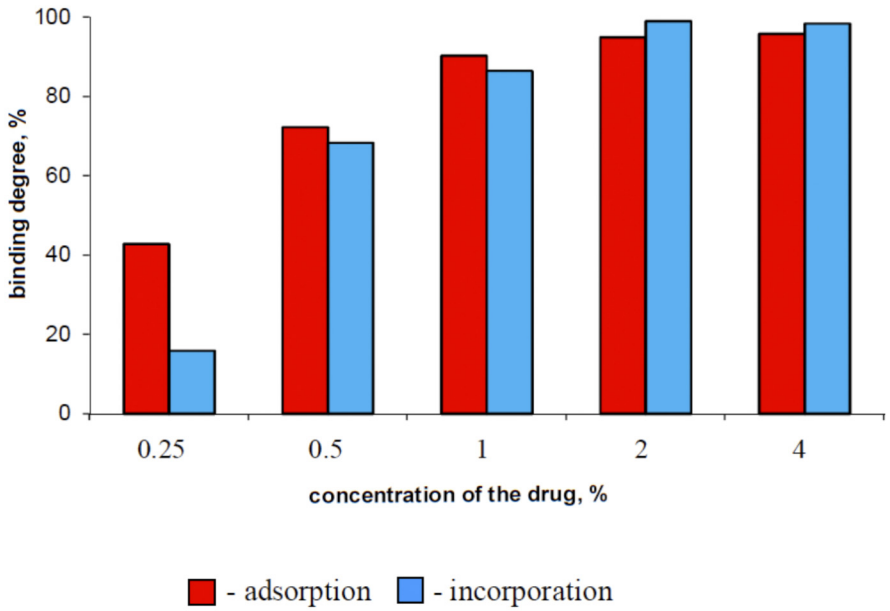

Figure 7: Adsorptive binding and incorporation of antiTB drug PASA into HSA nanoparticles.

to attain high loading efficiency for both drugs, which shows the perspective of using nanoparticulate forms of these drugs [136, 137]. Dependence of binding degree on the concentration of added PASA is shown on the graph (Figure **7**).

Drug Release from HSA Nanoparticles

Biodegradability of HSA nanoparticles and the accompanied drug release are mainly governed by the degree of crosslinking [35-37]. Drug release profiles from HSA nanoparticles are dependent on the amount of drug attached to the surface as well as incorporated in the inner part of the nanoparticles [1, 35-37]. For instance, the study of the drug release profile of obidoxime from HSA nanoparticles has shown that only the portion of the drug which was bound at or near the surface of nanoparticles has been released [121, 122]. Less than 25 % of obidoxime incorporated into the HSA nanoparticles released from polymeric nanoparticles within the time observed (2 hours), whereas the same amount of drug adsorbed on the particle surface released within the first 10 min [121, 122] (Figure **8**). However both systems are shown to be suitable nanoparticulate carriers for obidoxime [121, 122].

El-Samalagy M. and Rohdewald P. have synthesized HSA nanoparticles loaded with triamcinolone, dactinomycin and doxorubicin [125]. The drug uptake was found to be similar for the particles obtained by both adsorption and incorporation methods. The drug release occurred mainly as a result of desorption, although 20 % slower release profile has been observed in case of incorporation than when using particles obtained by adsorption [125].

The most suitable method for the study of drug release from HSA nanoparticles obtained by adsorption of drug on preliminary prepared empty particles seems to be dialysis, as the separation of nanoparticles from solution may lead to the loss of some part of the drug by desorption [1].

5. NANOSOMAL SYSTEMS BASED ON POLY-D,L-LACTIC ACID

One of the other perspective drug carriers used in developing controlled release systems is PLA and its copolymer with glycolic acid [111-113, 116, 138, 139]. First synthetic polymer and bioabsorbing material was polyglycolic acid which opened this class of polymers in 1954. Since that time the derivatives of this polymer polylactic (polylactide) and glycolic acids and ε-caprolactone have been used for the drug delivery purposes [113, 116, 138]. Polylactide is biocompatible and biodegradable polymer which has been used in medicine for a long time not only as auxiliary material, but as carrier for the targeted delivery of the drugs.

The best properties however possess the copolymer of PLGA [139]. Micro- and nanoparticles based on polylactic, polyglycolic acids and their copolymers and ethers are used for the delivery of various nature [139, 140, 141]. Depending on the ratio of lactic and glycolic acids it is possible to change such properties of the product as plasticity, durability, the biodegradation time and release rate of the drug. It has been found that varying the ratio of the lactic and glycolic chains the release rate of the drug can be controlled [142]. With increasing the content of glycolic chains the release rate of hydrophilic drugs increases and the lipophilic drugs decreases provided that the

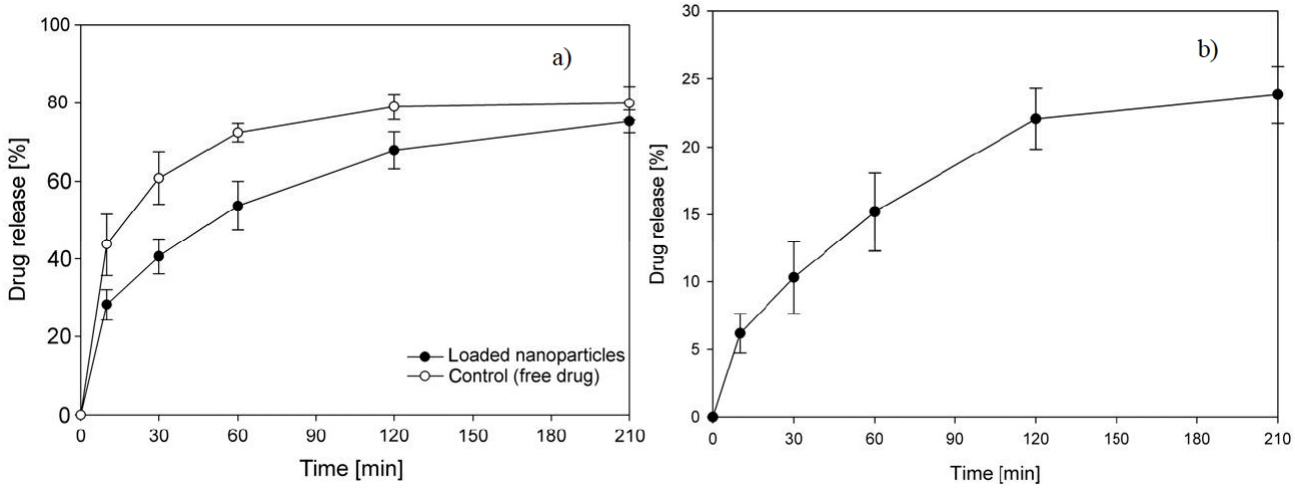

Figure 8: Release profile (mean±SD) of obidoxime dichloride from HSA nanoparticles obtained by adsorption method (a) in comparison to the free drug solution and by incorporation method (pH =10) (n=3) [121, 122].

drug excretion takes place as a result of polymer degradation. This way the copolymers of polylactic-co-glycolic acid with PEG and poly-caprolactone with controlled degradability have been successfully synthesized [142]. They degrade by the ester bonds to the derivatives of lactic and glycolic acids. It has been established that polylactides with hydrophobic end groups degrades 2.7 times faster *in vitro* and 4 times faster *in vivo* than the polymers with hydrophilic groups [143].

Antitumor drug preparations based on nanoparticles of the copolymers of lactic and glycolic acids which are allowed to the use in medicine practice in Russian Federation by the trade names dekapeptyl, zoladex, sandostatin and somatulin [144]. The copolymer of lactic and glycolic [50/50 Poly(DL-lactide-co-glycolide) (nominal)] acids is non-toxic and their catabolism ends up with the formation of CO_2 and H_2O [27, 144, 145].

Among the effective and reproducible methods of obtaining nanoparticles and nanocapsules of PLA, PLGA or their copolymers is found to be nanoprecipitation [146-154]. This method was first developed by Fessi *et al*. for the preparation of polymeric nanoparticles [148]. The system of nanoprecipitation mainly consists of three components, these are the polymer, the solvent of the polymer and non-solvent of the polymer [146, 148]. PLA nanoparticles with the range of particle size from 100 to 300 nm have been synthesized depending on the solvent and surfactant used [148, 150].

PLGA nanoparticles coated with transferrin with the size in the range 63-90 nm for the purpose of passing through blood-brain-barrier have been successfully synthesized in the presence of Tween 20 by nanoprecipitation method [151]. Nehilla B.J. *et al*. have synthesized coenzyme Q10-loaded PLGA nanoparticles without using surfactant with the average size 165 nm [152]. Nanoprecipitation method has also been used for the encapsulation of curcumin into PLGA nanoparticles by Yallapu M.M. *et al*. [153] as a result of which the particles with the size ranging in 95-560 nm have been obtained.

The mechanism of intracellular uptake of PLGA nanoparticles and their effect on therapeutic efficiency of the active compounds in cellular level when encapsulating DNA, proteins and different low molecular weight compounds are throhoughly considered by Panyam J. and Labhasetwar V. in [139].

The examples of using PLA and PLGA nanoparticles in treatment of tumor and tuberculosis diseases was shown above.

Helle A. *et al*. investigated the possibility of using capillary electrophoresis for the quantitative determination of model drugs (salbutamol sulphate, sodium chromoglycate and beclomethasone dipropionate) which were encapsulated in PLA nanoparticles by nanoprecipitation method [147]. A quantitative capillary electrophoresis method has been developed for salbutamol sulphate and sodium chromoglycate by the authors. It was found out that the encapsulation of beclomethasone dipropionate in the PLA nanoparticles was more efficient than in case of more hydrophilic model drugs (salbutamol sulphate and sodium chromoglycate) [147].

Burkeev M.Zh. *et al*. used the same method (nanoprecipitation) for encapsulation of widely used antiTB drug isoniasid in PLA nanoparticles [154]. Optimal conditions (solvent, the ratio polymer:drug, etc.) of synthesizing PLA nanocapsules loaded with the drug have been found. Nanoparticles of PLA loaded with the drug with the average diameter 200-300 nm and high binding degree (50 %) have been successfully synthesized. The system was found to be stable within the time which was confirmed by measurement of the surface charge of nanoparticles (-30-35 mV).

CONCLUSION

One of the major goals of pharmaceutical research is the development of drug formulations which are able to perform targeted delivery of drugs into specific organs or tissues [1, 2]. The drug taken systematically provides high efficacy, but at same time side reactions related to high dosage of the drugs appear as well. The concept of the “Magic Bullet” suggested by Paul Ehrlich at the end of 19^{th} century [2, 8] was the start of breakthrough research in medicine aiming at the development of systems with improved properties for transporting the drugs at the right parts of the human body. However the attempts on synthesizing the systems which are able to carry out targeted drug delivery started in the end of 60s of 20^{th} century by the group of prof. Peter Speiser and within about 40 years there were numerous works on the creation of “ideal drug delivery system” by combining varieties of biocompatible polymers with the drugs used in treatment of diabetes, tumors, tuberculosis and so on [3-79, 90, 102, 103, 112, 124, 125, 132, 133, 136-138, 154].

Numerous publications of the last three decades show the potential of using drug formulations of prolonged action which are created on the basis of polymeric nanoparticles and nanocapsules [1-154]. Prolongation of drug efficacy is accomplished by sustaining constant concentration of the drug in the targeted organs by increasing the stability and improving bioavailability of the drug. This gives the opportunity to decrease considerably the dose of the drug for the treatment of the disease [3-100]. Development of such systems for potent drugs offers a number of benefits over conventional drug formulations such as decrease of toxic reactions caused by a high dose of drugs, maintenance of therapeutic concentrations of the drug within a certain period of time (prolonged drug release).

Nanoparticles seem to be very promising drug delivery systems for a variety of drugs, especially for those to which oral and/or inhalable administration cannot be applied. In addition, nanoparticles can help in targeted delivery; the submicron size of the nanoparticles gives them the ability to cross narrow junctions and blood capillaries which can not be done when using microparticles.

The review given in this article is far from being comprehensive, however the authors tried to cover all aspects of synthesizing and characterization of nanoparticulate systems on the basis of such commonly used polymers as polyalkyl cyanoacrylates, polylactic acid and human serum albumin. The results of the investigations of the past 30 years devoted to the synthesis and study of polymeric nanoparticles and nanocapsules in treatment of tumors and tuberculosis using PACA, PLA and HSA evidence the importance and potential of application of such systems in drug targeting. There are some examples of nanosomal systems based on these polymers which have already passed clinical trials and are used for the targeted delivery of the drugs.

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Received on 07-03-2014 Accepted on 05-05-2014 Published on 25-06-2014

DOI: http://dx.doi.org/10.6000/1929-5995.2014.03.02.2