REVIEW

Poly(alkyl cyanoacrylate) nanoparticles as drug carriers: 33 years later

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First prepared in 1979, the colloidal nanoparticles based on biocompatible and bioerosive poly(alkyl cyanoacrylate) materials are still under investigation and hold promise for the development of novel formulations for targeted drug delivery. Different types of poly(alkyl cyanoacrylate) nanoparticles have been developed during the last 33 years, such as nanospheres, nanocapsules, hybrid magnetic-polymer nanoparticles, long-circulating nanoparticles, as well as nanoparticles functionalized with targeting ligands. A great variety of bioactive compounds have been loaded on poly(alkyl cyanoacrylate) nanoparticles, such as cytostatics, antibiotics, antiviral agents, anti-fungal drugs, non-steroidal anti-inflammatory drugs, bioactive proteins, nucleotides, etc. Therefore, this review cannot be and is not intended to be a complete review of all the research that has been done in this area, but just to bring together the basic concepts and ideas related to the preparation and applications of poly(alkyl cyanoacrylate) nanoparticles as drug carriers, emphasizing on the most important findings and discussing the future perspectives.

Keywords: drug delivery; nanoparticles; poly(alkyl cyanoacrylate)

Dr. Georgi Yordanov is working as an assistant professor at the Faculty of Chemistry and Pharmacy at Sofia University "St. Kliment Ohridski", where hold lectures in "Pharmaceutical nanotechnology" and "Nanotechnology in biology, pharmacy and medicine". He has specialized in Spain (University of Vigo), Japan (Meiji University) and Slovakia (Slovak Academy of Science). For his research work Dr. Yordanov has received numerous awards – award for young scientist in polymer science "Prof. Ivan Shopov" (Union of chemists in Bulgaria and the Institute of polymers, BAS, 2010), "Prof. Berndt Artin Vessels" Award (German Foundation for promotion of Bulgarian higher education, 2004) and nomination for the "Pitagor" award for young scientist (Bulgarian Ministry of Education, Youth and Science, 2011). The scientific interests of Dr. Yordanov are mainly in the field of biomedical nanotechnology, including development of novel colloidal formulations of anticancer drugs and antibiotics.

Contents:

1. Introduction

It has been shown that the use of colloidal systems for drug delivery could change the pharmacokinetics of different drugs, which may result in improved therapeutic index [1-10]. Such drug carriers include polymeric micelles, nanoparticles (made of biodegradable synthetic polymers, proteins or lipids), liposomes, niosomes, dendrimers, nanoemulsions, magnetic nanocarriers, multifunctional nanosized carriers, etc. These usually represent spherical colloidal structures of submicron size, which must be biodegradable and stable in body fluids, not causing systemic toxicity, embolism and immune response. In the ideal case, these nanocarriers can be loaded with various drugs and targeted to a pathological location in the body, providing increased bioavailability of drugs, decreased effective dose, protection of unstable drugs, achieving high drug concentration in infected or abnormal cells and low concentration in normal cells thus decreasing the drug toxicity and undesirable side effects. Many different synthetic polymers have been found to be suitable for preparation of various drug nanocarriers – poly(lactic acid), poly(alkyl cyanoacrylate), poly(ε-caprolactone), etc. Each of these polymers has advantages and disadvantages, which should all be taken into account when designing new drug delivery systems.

In this review the poly(alkyl cyanoacrylate) (PACA) colloids are consider as drug delivery systemsed. First prepared by emulsion polymerization in 1979 [11], the colloidal nanoparticles based on biocompatible and bioerosive PACA materials are still under investigations and hold promise for the development of novel formulations for targeted drug delivery [12-20]. The highly reactive alkyl cyanoacrylate monomers are approved for human use as surgical glues [21]; butyl cyanoacrylate is used as surgical glue in Bulgaria. These monomers are highly reactive and can be polymerized via anionic, zwitterionic or radical mechanism in suitable polymerization medium to form various types of nanocarriers – nanospheres, core-shell nanoparticles (with covalently attached hydrophilic polymers on the surface), nanocapsules (with oily or aqueous core), hybrid nanoparticles with magnetic core, etc. (*Fig. 1*). Effective method has been developed for large-scale sterilization of the nanoparticle formulations by gamma-radiation has been developed [22,23]. Different types of PACA-based nanocarriers, incorporating a great variety of drugs, such as cytostatics, antibiotics, antiviral agents, anti-fungal drugs, non-steroidal anti-inflammatory drugs, etc. Despite many *in vitro* and *in vivo* preclinical studies and few clinical trials, no formulation with these nanocarriers reached regular clinical application to date, which raises the question is there a real potential use for these nanocarrier system [24]. This has been attributed to the fact that a number of factors may interfere with the reproducibility of *in vitro* and *in vivo* results, which impedes the comparison of the many experiments done with PACA nanoparticles [24]. This review considers the current status and the challenges of using PACA nanoparticles as drug delivery systems. It is mainly intended to bring together the basic concepts and ideas related to the preparation and potential applications of PACA nanoparticles, emphasizing on the most important findings and discussing the future perspectives.
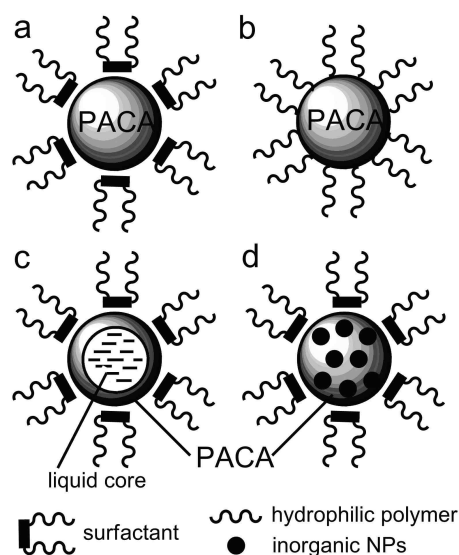

Figure 1. Schematic illustration of various types of PACA-based nanocarriers: **a**) nanospheres with adsorbed surfactant molecules; **b**) core-shell nanospheres; **c**) nanocapsules with adsorbed surfactant molecules; **d**) hybrid nanoparticle with adsorbed surfactant molecules.
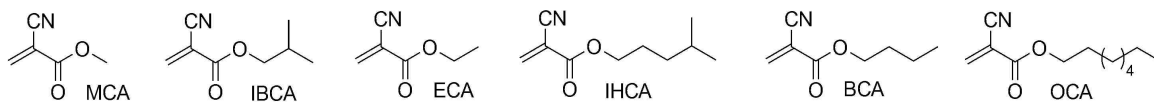
Figure 2. Chemical structures of some alkyl cyanoacrylate monomers used for the preparation of nanoparticles and their abbreviations: methyl cyanoacrylate (MCA); ethyl cyanoacrylate (ECA); butyl cyanoacrylate (BCA); isobutyl cyanoacrylate (IBCA); isohexyl cyanoacrylate (IHCA); octyl cyanoacrylate (OCA).

2. Methods for preparation

2.1. Polymerization-based methods

Alkyl cyanoacrylate monomers are highly reactive due to the combination of two electron-withdrawing groups (ester and nitrile) bonded to the same carbon atom. The structure of some alkyl cyanoacrylates, which are used for the preparation of nanoparticles, are shown in *Fig. 2*. The combination of the two electron-withdrawing groups leads to polarization of the C=C bond that is likely to be attacked by anions and compounds with nucleophilic groups (such as amines). Although the polymerization reaction proceeds quite rapid, it has been possible to determine the kinetics and mechanism of alkyl cyanoacrylate polymerization [25-32]. It is noteworthy that most of the preparation protocols reported so far are based on polymerization in aqueous medium, where the hydroxide ion is the initiator of the reaction [31]. A schematic illustration of the anionic polymerization of alkyl cyanoacrylates is given in *Fig. 3*. Most of the reported preparations of PACA-based nanoparticles in aqueous medium by polymerization-based methods proceed via anionic mechanism. For better control of the polymerization reaction, the aqueous polymerization medium contains acidic additives to decrease the pH, respectively to decrease the concentration of the hydroxide ions. If a compound with nucleophilic groups (for example, the drug to be loaded in to the nanoparticles) is present in the polymerization medium, it can attack the monomer molecule, leading to initiation of zwitterionic polymerization [33-36]. In this case the drug molecules become covalently associated with the polymer backbone. Such reactive drugs could be loaded on PACA nanoparticles by using the nanoprecipitation approach (see section 2.2).
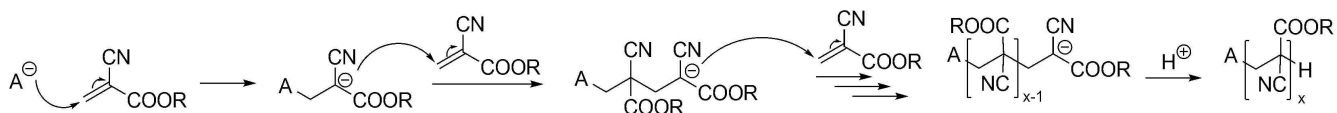
The classical approach for the preparation of PACA nanospheres is the emulsion polymerization in aqueous medium [11]. The method is based on the polymerization of the monomer in acidic (pH ~ 3) aqueous medium containing a suitable colloidal stabilizer, which is approved for biomedical applications (such as poloxamer 188, polysorbate 80, dextran, etc.). The chemical reaction proceeds via anionic mechanism, but the mechanism of nanoparticle formation seems to be quite complicated and still not fully understood. The mechanism of particle formation appears to take place in three separate steps, as described by Behan *et al.* [32]. Initially, oligomeric species are produced in the monomer droplet and are then terminated by the acid inhibiting agents present in the monomer (which seems to be the step that may lead to batch to batch variation in oligomer molecular mass and thus particle size). In the second step aggregation of the oligomeric units is followed by their swelling with monomer. The third and final step consists the *in situ* re-initiation of terminated oligomeric units by live chains followed by further polymerisation until equilibration of molecular mass is reached [32]. Various factors, such as pH of polymerization medium, the presence of inhibitors in the monomer, the concentration of monomer, the type of colloidal stabilizer, the type of drug and its concentration, all may have an effect on the molecular mass of polymer formed and the size of obtained nanoparticles [37-41]. In most of the cases the molecular mass is less then 5-10 kDa [42], which is required for the products of the particle biodegradation to be successfully eliminated. Various surfactants that are approved for pharmaceutical applications are used as colloidal stabilizers (polysorbate 80, poloxamer 188, etc.). The colloidal stabilizers prevent nanoparticle aggregation by adsorption on the nanoparticle surface, and thus providing steric repulsion between the particles. Various dextrans (which are not

Figure 3. Polymerization of alkyl cyanoacrylates by anionic mechanism.

amphiphilic and cannot form micelles) also have found application as stabilizers for nanoparticle dispersions, although our experience shows that nanoparticles obtained in some cases are usually larger (with wider size distribution) and less stable. A representative scanning electron microscopy (SEM) image of pure PBCA nanoparticles prepared in our laboratory using emulsion polymerization is shown in *Fig. 4a*. These nanoparticles are formed after polymerization (for 3 h) in aqueous polymerization medium, containing poloxamer 188 and citric acid (pH ~ 3) at monomer concentration of 1% (w/w). Drugs can be loaded in PACA nanospheres by entrapment in the polymer matrix of the particles during the polymerization or by adsorption on the surface of pre-synthesized particles [13]. Usually adsorbed drugs are usually more weakly bounded and are released faster than the entrapped drugs.
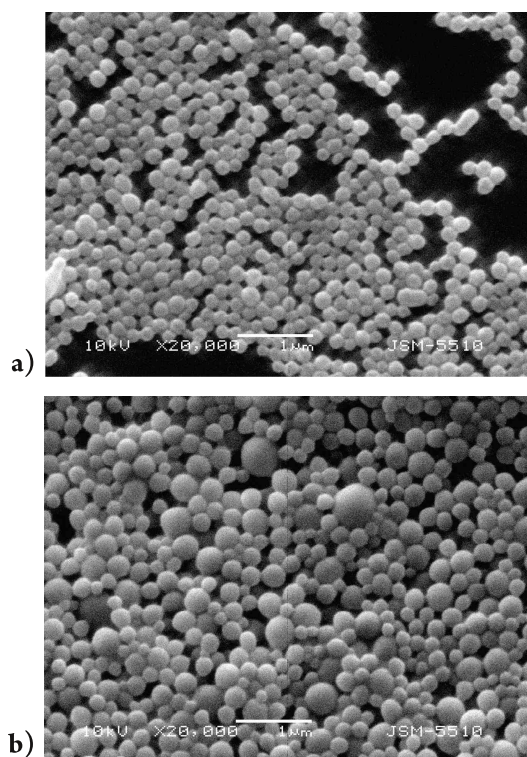

a)

b)

Figure 4. SEM images of PBCA nanoparticles prepared by: **a**) emulsion polymerization in the presence of citric acid and poloxamer 188; **b**) nanoprecipitation in the presence of poloxamer 188.
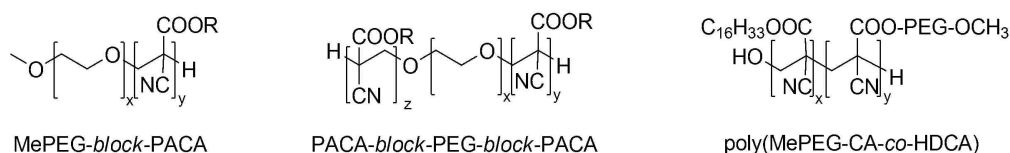
Polysaccharide-decorated PACA nanoparticles have been prepared in aqueous medium via redox radical emulsion polymerization [43-49]. This polymerization has been carried out in the presence of Ce(IV), nitric acid and various polysaccharides. The surface of the nanoparticles can be modulated by the nature, and the molecular mass of the polysaccharide used as stabilizer of the polymer colloids. Drugs, such as doxorubicin, can be loaded by adsorption on the nanoparticle surface [49].

Zwitterionic polymerization has been used to prepare PACA-based nanospheres of the core-shell type with covalently attached poly(ethylene glycol) (PEG) chains on the nanoparticle surface (so-called PEGylated nanoparticles) [50-53]. The polymerization has been carried out at low pH in the presence of PEG or methoxy-PEG (MePEG). The authors suggested that at these conditions the polymerization of alkyl cyanoacrylate is initiated by the hydroxyl group(s) of PEG and MePEG, and resulted in the formation of amphiphilic block copolymers PACA-*block*-PEG-*block*-PACA and MePEG-*block*-PACA, respectively (see *Fig. 5*). The obtained copolymers are amphiphilic and it was supposed that at the nanoparticle surface their PEG-blocks form chains or loops oriented toward the aqueous phase, thus providing hydrophilic surface and steric stabilization of the nanoparticles. Similar strategy has been utilized for the development of PEGylated PBCA nanocapsules [53]. These preparations were all performed at low pH (~ 1) in order to be minimized the concurrent initiation of the reaction by the hydroxide ions to be minimized. The cellular uptake and targeting abilities of nanoparticles could be influenced greatly by the PEG-coating. The adsorption of proteins on the nanoparticle surface of PEGylated nanoparticles is less pronounced leading to decreased uptake of the particles by the cells (for which reason PEGylated nanoparticles are frequently called "stealth" particles) of the reticuloendothelial system and increased circulation life-times in blood [52-55]. Yet the nanoprecipitation approach allows yet another strategy for the preparation of PEGylated PACA nanoparticles (see section 2.2).

Interfacial polymerization technique has been used

MePEG-*block*-PACA　　　PACA-*block*-PEG-*block*-PACA　　　poly(MePEG-CA-*co*-HDCA)

Figure 5. Chemical structures of various PACA-based copolymers (see the text for details).

for the preparation of nanocapsules and hybrid (organic-inorganic) composite PACA-based nanoparticles. This process takes place at the interface between two phases. It has been used for the preparation of nanocapsules, consisting of oily or aqueous core, surrounded by polymer membrane [56-59]. Oil-containing nanocapsules could be carriers of lipophilic molecules, whereas hydrophilic ones are efficiently encapsulated into water-containing nanocapsules. Oil-containing nanocapsules can be prepared by adding acetone solution of monomer and suitable oil into aqueous solution of colloidal stabilizer under vigorous stirring, leading to small oil/monomer droplets; the polymerization starts at the water/monomer interface initiated by hydroxide anions presented in the water [56,57]. For successful preparation of nanocapsules it is important that the polymer is insoluble in the organic oil. Nanocapsules with aqueous core have been prepared by addition of monomer solution to water in oil (w/o) microemulsion [58,59]. PEGylated nanocapsules have been prepared by similar strategy in the presence of PEG at low pH [53]. The main problem in these protocols is that nanospheres are obtained together with the nanocapsules and optimization of the solvent/oil ratio is usually required to minimize the formation of nanospheres. Preparation of nanocapsules from pre-synthesized polymer by interfacial deposition also has been reported (see section 2.2).

Interfacial polymerization has been used for the preparation of various hybrid (organic-inorganic) composite nanoparticles that contain inside small inorganic nanoparticles with specific functionalities. Magnetic nanoparticles have been incorporated in PACA colloids with the aim to control the drug release rate and particle localization by using external electromagnetic fields [60-64]. We recently have developed new types of hybrid inorganic/PACA nanoparticles for bioimaging applications by using quantum dots as fluorescent labels [65]. Later, quantum dot-loaded PEGylated PACA-based nanoparticles for *in vitro* and *in vivo* imaging have been prepared by Nicolas *et al.* [66]. Hybrid nanoparticles, containing zinc oxide (ZnO) cores, were also recently developed in our laboratory [67].

2.2. Nanoprecipitation

The nanoprecipitation approach for preparation of polymer colloids is a well-known technique in polymer science [68-70]. For the preparation of aqueous dispersions of polymer nanoparticles the polymer (which is not soluble in water) is dissolved in water-miscible organic solvent and is added to the aqueous medium thus resulting in phase separation of the polymer in the form of nanoparticles. The polymer particles are formed spontaneously and the organic solvent is then removed by evaporation. If the polymer is amphiphilic there is no need of additional colloidal stabilizer in the aqueous medium. Such a technique has been applied for the preparation of PEGylated nanoparticles composed of poly[methoxy-poly(ethylene glycol)-cyanoacrylate-*co*-hexadecyl cyanoacrylate] amphiphilic copolymer, poly(MePEG-CA-*co*-HDCA) [71-82] (*Fig. 5*). Such PEGylated nanoparticles have been loaded with fluorescent quantum dots for bioimaging [66], with anticancer drugs for delivery to the brain [79], etc. Importantly, it has been found that such nanoparticles are less recognizable by the cells of reticuloendothelial system (RES) and could be used for drug targeting to solid tumours via the EPR effect [52-55] (see section 4.3).

Recently, we have adapted the nanoprecipitation method in order to prepare pure and drug-loaded poly(butyl cyanoacrylate) (PBCA) nanoparticles [83]. In our experiments we have used PBCA with molecular mass Mw ~ 2 kDa, which is soluble in acetone. As colloidal stabilizers we have used dextran (~ 40 kDa), poloxamer 188 or polysorbate 80. The pure PBCA nanoparticles obtained by nanoprecipitation are usually 200-300 nm in size (*Fig. 4b*). We have utilized the nanoprecipitation technique to entrap chlorambucil [83], epirubicin [84] and econazole [85] in PBCA nanospheres. The nanoprecipitation method for preparation of PACA-based nanoparticles has the advantage that the used pre-synthesized polymers are well-characterized and their characteristics do not depend on the conditions of the nanoparticle formation. This approach could be useful also for the entrapment of highly sensitive and/or reactive drugs, which could initiate zwitterionic polymerization or are unstable in the acidic medium of the classical emulsion polymerization. The nanoprecipitation method has also been adapted for the preparation of PACA-based nanocapsules by interfacial deposition of presynthesized polymer between the aqueous medium and the oily nano-droplets [86-88].

3. Mechanisms of drug release

There are different mechanisms of drug release depending on the type of drug loading in nanoparticles

[13,17] (*Fig. 6*). Drugs that are adsorbed on the surface of pre-synthesized nanoparticles are released by desorption. Entrapped drugs, which are weakly bounded to the polymer material, are released by diffusion. Drugs, which have high affinity to the polymer are released very slowly by diffusion and can be released during the bioerosion of the polymer. It has been shown that enzymes, which enhance the rate of nanoparticle erosion (by enhancing the hydrolysis of ester bonds), also accelerate the drug release from PACA nanoparticles [89]. The main degradation pathway for PACA is the hydrolysis of the ester bond. The larger is the alkyl side chain – the lower is the degradation rate of the polymer [90]. In vitro methods for evaluation of the degradation rate of PACA nanoparticles have been developed [91] (the biodegradation of PACA nanoparticles is considered also in section 5).
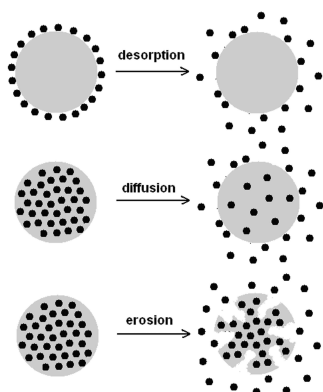

Figure 6. Illustration of the drug release from nanoparticles by desorption, diffusion and erosion. The drug molecules are represented by small black circles.

4. Biodistribution and drug targeting

4.1. Interaction of PACA-based nanocarriers with proteins from human blood plasma

Immediately after parenteral administration of nanoparticles into the organism they interact with proteins from the blood plasma. The rate and the strength of this interaction with the various proteins present in blood plasma largely determines the biodistribution pattern of the nanocarriers and therefore represents an important topic for scientific research [92-95]. The major proteins from blood plasma that have been found to interact with various PACA-based nanoparticles include albumin, fibrinogen, IgG, IgM, transferrin, complement factors and various apolipoproteins [74,96-98]. The chemistry of the nanoparticle surface largely determines the pattern of this interaction. More hydrophilic surfaces attract fewer amount of proteins. Therefore, the interaction of PEGylated nanoparticles with proteins has been found to be diminished in comparison with hydrophobic nanoparticles [74,96,97]. The nanoparticles of PACA homopolymers have relatively hydrophobic surfaces and adsorb larger amounts of proteins thus tending to be more easily recognized and internalized by phagocytic cells, because proteins like complement components and immunoglobulins serve as opsonins – substances that coat foreign objects and destine them for phagocytosis. Such nanoparticles could be suitable as drug carriers for antibiotics that need to be delivered to phagocytic cells (in cases of intracellular infections; see section 4.2) or other bioactive substances that need to be delivered to the cells of the reticuloendothelial system (RES). The PEGylated nanoparticles (composed of amphiphilic PACA-based copolymers) are less recognizable by the phagocytic cells and therefore are known as "stealth" carriers or long-circulating carriers (circulating for a long time the in blood stream, because are not captured by phagocytes) [52-55]. Such nanoparticles are suitable for cancer treatment via the so called enhanced permeability and retention (EPR) effect (see section 4.3). Another type of PACA-based nanocarriers combines the advantages of the "stealth" carriers (c.a. hydrophilicity) and ligands that make it possible to selectively recognize target cells (such as folate-modified nanocarriers that target cancer cells expressing the folate receptor; see section 4.3) [99-101]. The two main types of PACA-based nanoparticles (non-PEGylated and PEGylated) are schematically represented in *Fig. 7*.

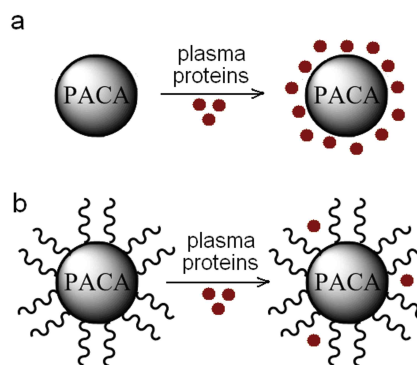**Figure 7.** Illustration of the interaction of plasma proteins (represented with small circles) with nanoparticles: **a**) nanoparticles of homopolymers interact strongly with proteins; **b**) PEGylated nanoparticles interact weakly with proteins.

4.2. PACA-based nanocarriers for delivery of drugs to phagocytic cells

It has been shown that entrapment of antibiotics in nanocarriers can improve the therapeutic index by targeting drug delivery to infected cells [10,13,102-107]. There, number of intracellular pathogens, such as salmonellosis, tuberculosis, listeriosis, etc., cause severe infections. These microorganisms have developed different survival mechanisms that make these infections difficult to eradicate [102,103]. The basic idea behind using antibiotic nanocarriers is to design a carrier system that is able to be endocytosed by infected phagocytes and then the antibiotic to be released into these cells. Macrophages could recognize opsonized nanoparticles as foreign species and nanoparticles could become entrapped in the phagolysosomes, thus becoming in close contact with the bacterial cells there [13]. The entrapment of ampicillin in poly(isohexyl cyanoacrylate) (PIHCA) nanoparticles was found to increase by 120-fold the antibiotic efficacy in experimental salmonellosis [104,108]. Other antibiotics have also been incorporated in various PACA-based nanocarriers [102,105-107,109-113]. Recently, we have developed ciprofloxacin-loaded PBCA nanoparticles, which allowed pH-controllable drug release [114]. Our preliminary susceptibility tests on a clinical isolate of *Escherichia coli* showed that ciprofloxacin-loaded PBCA nanoparticles are at least as active as the free drug [114]. Tests with ampicillin-loaded poly(isobutyl cyanoacrylate) (PIBCA) nanoparticles on infected macrophages, have shown that after 30 h of incubation the viable bacteria were reduced with 99 % as compared with controls, while the free ampicillin had a little effect [115]. *In vivo* experiments with mice have been performed, demonstrating the high efficiency of antibiotic-loaded PACA nanoparticles for the treatment of intracellular infections [13,104,115]. Similar ideas stand behind using nanocarriers loaded with antiviral agents [116-120]. The main problem to be considered in such biomedical applications of PACA nanoparticles is the overloading of phagocytic cells with excess of polymer material (as well as drug), which may lead to toxicity.

4.3. PACA-based nanocarriers for cancer chemotherapy

In order to obtain delivery systems for targeted cancer treatment (for detailed reviews see refs. [10,13,17]), various bioactive compounds (cytostatics, hormones,

peptides and nucleic acids) have been loaded in PACA nanocarriers. The nanoparticle surface can be specially designed in order to make the nanoparticles suitable for a particular cancer treatment. Usually, after intravenous administration, colloidal nanoparticles are cleared from the blood stream by the mononuclear phagocytic cells (MPC), mainly by the fixed macrophages of liver and spleen [121-123]. This may be utilized for passive targeting of drugs to the spleen, liver, lung, or bone marrow. Such nanoparticles, if loaded with anticancer agent, can be used for treatment of cancers that are localized in these organs. Although the drug-loaded nanoparticles do not reach directly the cancer cells, the phagocytes in the organs, where the nanoparticles become entrapped, may serve as drug reservoirs. It has been shown that the utilization of nanocarrier systems can improve drug targeting also to lymph nodes [124-127]. *In vivo* studies proved that PIBCA nanocapsules showed enhanced accumulation of drug in the lymph nodes, compared with other carriers such as emulsions and liposomes [126]. To enhance drug delivery to lymph nodes, various methods of surface modification of the nanocarriers have been studied, such as coating with poloxamines or poloxamers [128], although the rote of nanoparticle administration seems to be quite important for their biodistribution – lymphatic localization has been observed at subcutaneous and intraperitoneal administration of nanoparticles [124].

As described above, the uptake of nanocarriers by macrophages can be reduced by surface PEGylation [129-131]. The PEGylated nanocarriers when administered intravenously have longer blood circulation half-times. On the other hand, most solid tumours have
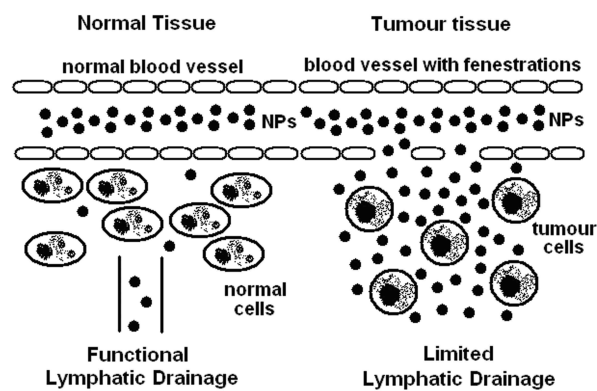

Figure 8. Schematic illustration of the EPR-effect used for passive targeting of nanoparticles to solid tumours.

unique pathological characteristics that are not observed in normal tissues and organs, such as extensive angiogenesis and hyper-permeable vasculature (fenestrations in the walls of blood vessels) and non-functional lymphatic drainage that causes retention of macromolecules and nanoparticles in the tumour tissue. This is known as the enhanced permeability and retention (EPR) effect [13,17] (*Fig. 8*). Drug-loaded nanocarriers therefore can penetrate through the leaky tumour vasculature, to accumulate and degrade in the tumour interstitium, releasing the loaded drug and creating its high local concentration.

The nanoparticle surface can be modified with targeting ligands (such as folic acid; *Fig. 9a*) that recognize a specific target thus achieving active targeting of the nanoparticle carrier system to cancer cells [99-101]. The idea behind decoration of nanocarriers with folate is that many cancer cells overexpress the folate-binding protein on their surfaces. However, one must keep in mind that normal actively dividing cells also express the folate receptor. It has been found that the folate-decorated nanoparticles interact more strongly with the folate-binding protein than the PEG-coated nanoparticles, which can be exploited for the selective targeting of different anticancer agents to cells that overexpress the folate receptor [99,100]. Recently developed highly functionalized PACA-based nanoparticles make it possible to decorate the particle surface with various desirable targeting ligands via azide-alkyne "click" chemistry [101] (*Fig. 9b*).
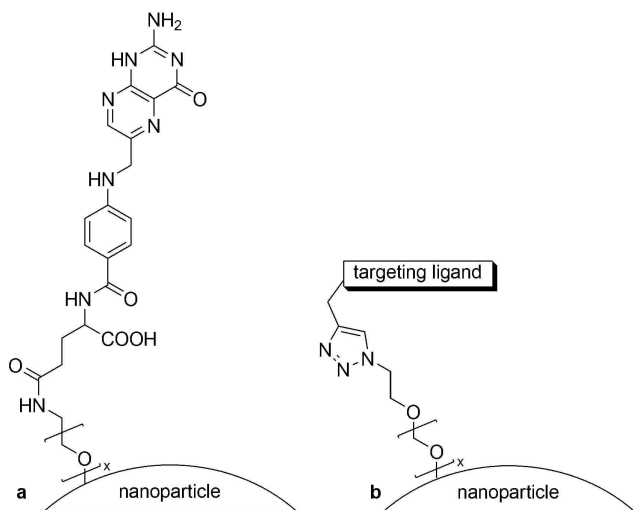

Figure 9. Schematic illustration of two different types of PACA-based nanoparticles for active targeting prepared by: **a**) modification with folate; **b**) using azide–alkyne "click" chemistry.

It has been shown that PACA nanoparticle carriers can be highly efficient for the treatment of multidrug-resistant cancer cells [132-134]. The mechanism may involve enhanced drug penetration into cells as well as inhibiting efflux of drug molecules from the resistant cells, although the exact mechanism is not completely clarified. For example, the utilization of doxorubicin-loaded PIHCA nanoparticles for treatment of resistant breast cancer cells resulted in 130-fold increase of the drug efficiency [132].

Only few PACA-based formulations for intravenous administration have been studied clinically although there are numerous preclinical studies. Kattan *et al.* [135] have conducted a phase I clinical trial of doxorubicin-loaded PIHCA nanoparticles in 21 patients with refractory solid tumours. Although unexpected side effects such as fever, bone pain, or allergic reactions were noted, they were well tolerated and were all rapidly reversible. In a recent clinical trial [136] was found that intravenous administration of mitoxantrone-loaded PBCA nanoparticles allows prolonged median survival periods (to 5.46 months compared to 3.23 months in controls) in patients with hepatic cancer.

4.4. PACA-based nanocarriers for drug delivery to the brain

The blood-brain barrier represents a physiological barrier that limits the transport of many different compounds (including various drugs, such as antibiotics and cytostatics) to the brain tissue. Therefore, finding suitable drug carriers that can overcome this limitation is important for the development of effective therapies for various brain diseases. It has been found that drug-loaded PACA nanoparticles can be targeted into the brain by modifying their surface with the surfactant polysorbate 80 [137-139]. This surfactant represents PEG-modified sorbitane monooleate. It has been supposed that these nanocarriers adsorb apolipoproteins E from blood plasma and then cross the brain endothelium via receptor-mediated endocytosis and transcytosis through the endothelial cells [138]. This makes the PACA nanoparticles possible candidates for drug carriers in the treatment of brain tumours. For example, doxorubicin-loaded nanoparticles with polysorbate 80-modified surface, when administered intravenously resulted in 40% cure in rats with intracranial transplanted glioblastoma [140]. However, when treating advanced brain tumours, one must take into account that nanoparticles can be

mainly localized in the tumour tissue rather via the EPR effect than by crossing the blood-brain barrier.

4.5. Hybrid PACA-based nanoparticles

Generally, two main types of composite hybrid (organic-inorganic) PACA-based nanoparticles have been developed: i) fluorescent composite nanoparticles, prepared by incorporating semiconductor nanoparticles (quantum dots); and ii) magnetic composite nanoparticles, prepared by incorporating magnetite nanoparticles. Fluorescent quantum dots represent small (usually few nanometres in diameter) nanocrystals composed of inorganic semiconductor material, which have found applications as fluorescent probes in bioimaging, especially where bright and stable fluorescent signal is required [141-143]. Such nanocrystals are usually hydrophobic (therefore are suitable for incorporation in the hydrophobic interior of colloidal nanoparticles) and have been used as fluorescent tags for colloidal drug carriers (PACA-based nanoparticles [65,66], liposomes [144], PLGA nanoparticles [145]) to visualize and investigate their interaction with living cells. Magnetic nanoparticles (of sizes usually below 100 nm) can be easily manipulated by using external magnetic fields and have a great capacity to find many applications in therapy and diagnostics [146]. Magnetic nanoparticles have been incorporated in PACA nanoparticles with the aim to achieve controllable drug release rate and particle localization by using external electromagnetic fields [60-64].

5. Biodegradation and toxicity

The cytotoxicity of PACA nanoparticles is usually correlated with the rate of biodegradation of the polymer backbone. The main products of biodegradation of PACA are poly(cyanoacrylic acid) and the corresponding alcohol, which are formed after hydrolysis of the ester bond [90]. Higher toxicity is usually observed in cases of higher biodegradation rate, which is related to the length of the alkyl side chain [147]. The PACA-based polymers with longer alkyl chain degrade slowly and are less cytotoxic. *In vitro* methods for evaluation of the degradation rate of PACA nanoparticles have been developed [91]. The adhesion of nanoparticles to the cell membrane can also increase the cytotoxicity by local release of biodegradation products in high concentrations

close to the cell membrane [148].

The toxicity of PACA-based nanoparticles is expected to depend on their physicochemical properties, which determine the actual biodistribution profile. Investigation of the liver toxicity of PACA nanoparticles shows slight modifications in the hepatic function after chronic administration of nanoparticles [149]. These effects have been found reversible when the treatment was stopped. Because the mononuclear phagocyte system is concerned, there is a potential danger for physical blockade of this tissue caused by systematic high-dose administration of nanoparticles [150,151].

It must be taken into account that utilization of nanoparticle drug carriers may be beneficial for decreasing some undesirable side effects of drugs, but the alteration of the drug biodistribution by its association with nanoparticles may cause new types of toxicity. For example, it has been shown that the incorporation of doxorubicin in PACA nanoparticles may reduce its cardio-toxicity, but may increase the bone marrow toxicity [152]. For example, unexpected side effects such as fever, bone pain, or allergic reactions were noted in a phase I trial with doxorubicin-loaded PIHCA nanoparticles, however they were well tolerated and were all rapidly reversible [135].

6. Conclusions

Now, 33 years after the first preparation of PACA nanoparticles, despite of reproducibility problems and insignificant number of clinical trials, there is still a potential for development of successful PACA-based formulations that will respond to all requirements for clinical use. It is expected that further research in this area will provide novel nano-formulations for treatment of severe diseases and will improve chemotherapy by targeted drug delivery. The future development of PACA nanoparticles could be directed toward two main goals. The first one could is the development of multifunctional nanoparticles incorporating various drugs for combined therapy, contrast agents for monitoring of the nanoparticle biodistribution, as well as some substances for improved drug action – efflux inhibitors (or other inhibitors of drug resistance), drug stabilizers and permeation enhancers. Such multifunctional nanoparticles could be decorated with targeting moieties toward specific cells and tissues and should provide better control of the drug release rate at the site of drug action. The second main goal could be encouragement of

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more preclinical and clinical trials with the currently developed advanced formulations, such as PEGylated and folate-decorated nanoparticles. Research could also be focussed toward the PACA-based formulations for topical and oral drug delivery, where there are less restrictive requirements for production and less risks of systemic toxicity. The development of such nanostructures is expected to improve the chemotherapy of many diseases in the future medical practice.

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REVIEW

Полиалкилцианоакрилатните наночастици като лекарствени носители: 33 години по-късно

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Колоидните наночастици на основата на биосъвместими и биоерозивни полиалкилцианоакрилатни материали са получени за първи път през 1979 г. и все още са обект на интензивни изследвания с цел разработване на нови лекарствени формулировки за насочено лекарствено доставяне. През последните 33 години са разработени различни видове полиалкилцианоакрилатни наночастици – наносфери, нанокапсули, хибридни полимерно-магнитни наночастици, дългоциркулиращи наночастици, както и наночастици, които са функционализирани с насочващи лиганди за активно целево лекарствено доставяне. Получени са формулировки с полиалкилцианоакрилатни наночастици на различни видове биологично-активни вещества – цитостатици, антибиотици, противовирусни агенти, противогъбични лекарства, нестероидни противовъзпалителни лекарства, биологично-активни протеини, нуклеинови киселини и др. Настоящият обзор няма за цел да бъде пълно и изчерпателно обобщение на всички получени до момента резултати, а цели да обобщи основните концепции и идеи, свързани с получаването и приложението на полиалкилцианоакрилатните наночастици като лекарствени носители, да изтъкне най-важните открития и да очертае бъдещите перспективи в областта.

Ключови дъми: лекарствено доставяне; наночастици; полиалкилцианоакрилат