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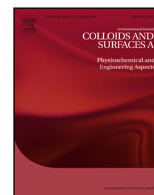

# Albumin-stabilized epirubicin nanocarriers of core–shell type based on poly(butyl cyanoacrylate) and poly(styrene-co-maleic acid)

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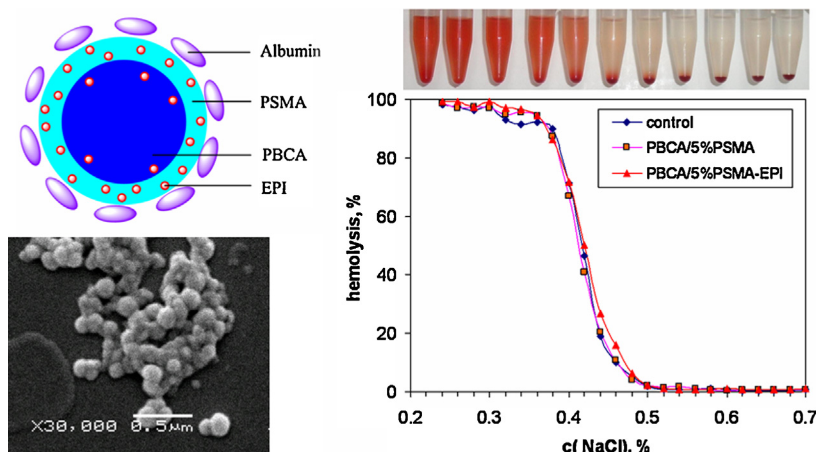
## HIGHLIGHTS

- Novel PBCA/PSMA colloids were prepared by nanoprecipitation.
- PBCA/PSMA colloids had high loading efficiency for epirubicin.
- Drug-loaded PBCA/PSMA colloids were successfully stabilized by albumin.
- The albumin-stabilized particles did not affect the erythrocyte cell membrane.

## GRAPHICAL ABSTRACT

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## ABSTRACT

This article describes a facile approach for preparation of novel albumin-stabilized polymer nanoparticles of core–shell type based on poly(butyl cyanoacrylate) (PBCA) and poly(styrene-co-maleic acid) (PSMA) as carriers for the anticancer drug epirubicin. The PBCA/PSMA particles were obtained by nanoprecipitation and were found to be spherical in shape, with monomodal size distribution and negative zeta-potentials. Particles of increasing average sizes between 100 and 200 nm were prepared by increasing the PBCA/PSMA ratio. Even 5 wt% of PSMA in the PBCA/PSMA particles resulted in increased electrostatic stabilization of the drug-free colloids and larger absolute value of the zeta potential. This effect on the electrokinetic behavior was attributed to enhanced deposition of the amphiphilic PSMA component at the particle surface and formation of a PSMA-enriched shell over the PBCA-enriched particle core. Epirubicin was loaded to the PBCA/PSMA particles by sorption. Only 5 wt% of PSMA in the PBCA/PSMA particles was enough to increase drug loading efficiency to ~95% and to improve albumin adsorption on the particle surface leading to increased colloidal stability. The obtained albumin-stabilized PBCA/PSMA epirubicin carriers did not cause any significant hemolysis (tested in vitro), neither affected the osmotic fragility of erythrocytes, which is an important prerequisite for biomedical applications.

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## 1. Introduction

Nanomedicine provides a platform for targeted drug delivery and improved therapeutic efficacy [1]. Ideally, utilization

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of nanocarriers can lead to improved pharmacokinetics of drugs, increased drug concentration in infected or abnormal cells, decreased drug toxicity and improved therapeutic index, which is expected to be highly beneficial especially for cancer chemotherapy [2–4]. Currently, there are three main strategies for targeting nanomedicines to solid tumors: (i) passive targeting via the enhanced permeability and retention (EPR) effect; (ii) active targeting to cells via specific receptors and ligands; (iii) utilization of nanomedicines with triggered drug release profile, the so-called stimuli–responsive carriers [5]. Each of these strategies has its advantages and disadvantages; however it appears that the EPR effect is the basis for successful realization of the other two approaches. This effect is based on the pathologic structure of blood vessels and the lack of lymphatic drainage in most solid tumors [6–8]. Tumor endothelia are often highly fenestrated, containing fenestration of sizes up to 600–800 nm, which make them permeable to nanocarriers (usually less than 200 nm in size). After passing through these fenestrations nanocarriers enter into the tumor interstitial space, where they can act directly upon cancer cells. Some nanocarriers have shown tumor endothelial toxicity. For example, nanocarriers of poly(styrene-co-maleic acid), PSMA, have demonstrated reduction of the tumor microvascular index by 40%, extensive vascular occlusion and necrosis, and increased tumor permeability [9].

There are two major problems with the successful utilization of the EPR effect in cancer treatment. First, most vessels in solid tumors are anatomically heterogeneous and often there are necrotic areas and thrombi inside large tumors, which compromises the effective penetration of nanomedicines through the entire tumor tissue [10]. For that reason, complete tumor eradication most often could not be achieved, because viable tumor cells remain around unaffected microvascular network [9]. Second, nanocarriers could be endocytosed by non-tumor cells before they have enough time to reach and effectively accumulate in the tumor. Various professional phagocytes (tissue macrophages, monocytes, neutrophils, etc.) and endothelial cells are known to internalize nanoparticles via endocytosis [11]. Endocytosis of nanocarriers by non-target cells leads to rapid decrease of nanocarrier plasma concentration and compromises their EPR-mediated accumulation in the tumor tissue. Internalization of nanocarriers into phagocytic cells and their overall biodistribution profile are known to be largely affected by protein adsorption on the nanocarrier surface [12–14]. Adsorption of opsonins (immunoglobulins, fibrinogen, complement components, etc.) results in rapid recognition of the opsonized nanoparticles and their phagocytosis by macrophages. Albumin, the most abounded plasma protein, is considered as an anti-opsonin [15], which suggests that its adsorption on nanoparticle surface may diminish phagocytosis of nanocarriers by macrophages. PSMA copolymers are known to have high affinity to albumin, which has been used to explain the relatively long circulation lifetimes of PSMA-based nanocarriers [16].

Previous reports have demonstrated that nanoparticles of poly(butyl cyanoacrylate), PBCA, could be suitable drug carriers for a variety of drugs, mainly anticancer agents [17–19]. Recent findings have shown that epirubicin loading to PBCA nanoparticles could lead to changed intracellular drug distribution in cervical carcinoma (HeLa) cells and suggested a possible shift from p53-dependent DNA/RNA intercalation-based induction of cytotoxicity by free epirubicin to a caspase-induced cell death by the epirubicin-loaded PBCA formulation [20]. However, the relatively hydrophobic nature of cyanoacrylate polymers is considered a major reason for adsorption of variety of blood plasma proteins, including opsonins, on their surface [14]. One strategy to decrease opsonin adsorption is to utilize poly(ethylene glycol) (PEG)-coated particles composed of PEG–PBCA copolymers [21,22]. Another strategy, proposed in this article, represents coating of nanoparticles with an anti-opsonin, such as albumin.

Our aim in this study is to construct novel albumin-stabilized colloidal nanoparticles of core/shell type composed of PBCA/PSMA. The idea for preparation of such a system is based on our hypothesis that the PSMA shell would serve as a linker between the PBCA particle core and albumin, which is to be adsorbed as an outer anti-opsonin shell. We attempted to prepare such particles by means of nanoprecipitation approach from pre-synthesized polymers and then to load epirubicin by sorption before final coating with human serum albumin. Nanoparticles of various PBCA/PSMA ratios were prepared and characterized for morphology, size-distribution, ζ-potential, chemical composition, and drug loading efficiency. Investigations of hemolysis and erythrocyte osmotic fragility were performed to evaluate the hemocompatibility of the obtained nanocarriers.

## 2. Materials and methods

### 2.1. Materials and reagents

Butyl cyanoacrylate (BCA) precursor was from Special Polymers Ltd. (Bulgaria). Poly(styrene-co-maleic anhydride) (according to manufacturer: Mn ~1900 by GPC; 75 wt% styrene, $T_g$ 125 °C), human serum albumin (HSA; lyophilized powder, >96%) and Pluronic F68 (poloxamer 188, Mn ~8350) were from Sigma–Aldrich (USA). Poly(styrene-co-maleic acid) (PSMA) and poly(butyl cyanoacrylate) (PBCA) were prepared according to previously described procedures [23,24]. Dextran 40 (from *Leuconostoc* ssp.; Mr ~40,000) was from Fluka (Denmark). All other reagents were of analytical grade. Distilled water was used in all experiments. Epirubicin hydrochloride (EPI.HCl) (produced by Synbias Pharma) was a gift from Actavis.

### 2.2. Preparation of drug-free PBCA/PSMA nanoparticles

Various amounts of PBCA and PSMA (a total mass of 50 mg) were weighted and dissolved in dry acetone (4 ml). The solution was dropwise added in aqueous medium (10 ml) containing dextran 40 (50 mg) upon intensive magnetic stirring. After formation of particles, the acetone was evaporated and the final volume of the dispersion was adjusted at 9 ml by addition of distilled water. The pH was fixed at 7.4 and the ionic strength at 0.150 M by addition of 10× PBS (1.0 ml). The obtained dispersion was sonicated and filtered through porous glass filter (G1) to remove polymer aggregates (if any). Pure PBCA nanoparticles obtained by this procedure were unstable and aggregated easily after acetone evaporation. For their stabilization, poloxamer 188 (40 mg) was added and the obtained dispersion was sonicated for 5–10 min.

### 2.3. Preparation of EPI-loaded and albumin-coated PBCA/PSMA nanoparticles

Epirubicin-loaded nanoparticles were prepared from the drug-free ones by sorption of the drug at room temperature in phosphate-buffered saline. For that purpose, 870 μl of the obtained PBCA/PSMA dispersions was mixed with 30 μl of aqueous solution of EPI.HCl (10 mg/ml) and 0.1 ml PBS. The obtained mixtures were sonicated and let to equilibrate overnight at room temperature (25 °C). Samples with low amount of PSMA (below 20%) formed precipitated aggregates after mixing with EPI and could be stabilized after addition of albumin. Albumin-coated nanoparticles were obtained by HSA adsorption on the surface of the EPI-loaded particles at HSA concentration of 10 mg/ml. After mixing of HSA and nanoparticles, the obtained dispersions are sonicated for 10 min and stored at 4 °C until analysis by DLS (within 24 h).

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