Colloids and Surfaces A 538 (2018) 238–249

Contents lists available at ScienceDirect

Colloids and Surfaces A

journal homepage: www.elsevier.com/locate/colsurfa

Research paper

Structural changes on polymeric nanoparticles induced by hydrophobic drug entrapment

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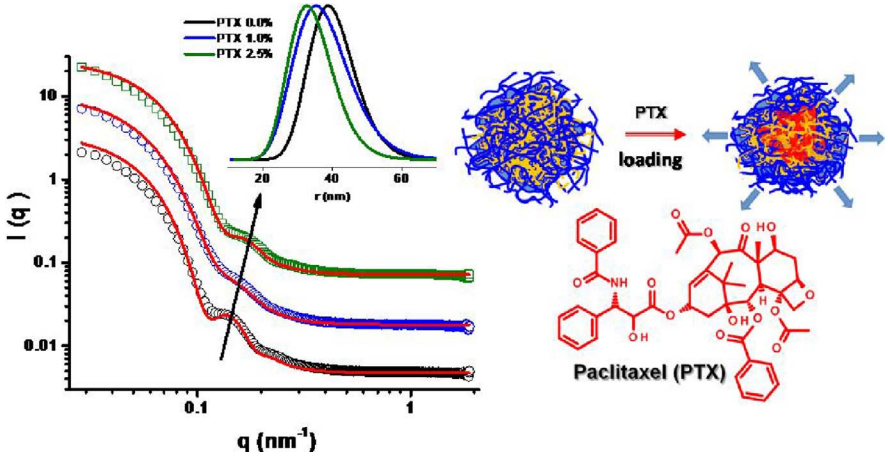
GRAPHICAL ABSTRACT

Several scattering techniques (DLS, SLS, SAXS) and transmission electron microscopy (TEM, cryo-TEM) were used to probe how the entrapment of a hydrophobic drug molecule modifies the inner structure of polyester nanoparticles.



ARTICLE INFO

Keywords:
Polymer nanoparticles
Drug delivery
Paclitaxel
DLS/SLS and SAXS

ABSTRACT

The potential use of polyester polymeric nanoparticles (NPs) as drug nanocarriers is well-documented. Nevertheless, structural changes due to hydrophobic drug loading and release have been rarely explored. Herein, we have used static and dynamic light scattering (SDLS), small-angle X-ray scattering (SAXS), transmission electron microscopy (TEM) and cryo-TEM to probe how the entrapment of a hydrophobic drug molecule changes the nanoparticles feature. The presence of the hydrophobic drug molecule modifies the inner structure of the

Abbreviations: PBSBDL, poly[(butylene succinate)-*co*-(butylene dilinoleate)]; PLA, poly(D,L-lactide); PLGA, poly(D,L-lactide-*co*-glycolide); R_G, radius of gyration; R_H, hydrodynamic radius; ρ, R_G/R_H ratio; PTX, paclitaxel; *d*, density; d_{NP}, density of the nanoparticles; *R*, small angle x-ray scattering radius; PBS, poly(butylene succinate); PBDL, poly(butylene dilinoleate); M_n, number average molecular weight; M_w, weigh average molecular weight; M_w/M_n, dispersity; BS, butylene succinate; BDL, butylene dilinoleate; B, degree of randomness; ϕ_{water}, water fraction of the nanoparticles; $M_{w(NP)}$, molecular weight of the nanoparticles; *p*(r), pair-distance distribution function; ζ, zeta potential; χ, Flory-Huggins interaction parameter; δ, solubilty parameter

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http://dx.doi.org/10.1016/j.colsurfa.2017.10.059
Received 13 August 2017; Received in revised form 23 October 2017; Accepted 24 October 2017

NPs. The polymeric assemblies are characterized by differences in their densities (~ 0.06 g cm^{-3} for poly(D,L-lactide) – PLA or poly(D,L-lactide-*co*-glycolide – PLGA) and 0.46 g cm^{-3} for poly[(butylene succinate)-*co*-(butylene dilinoleate)] – PBSBDL). They are thus water swollen in the drug-free condition. The NPs were further prepared by using the same polyesters and given amounts of the poorly water-soluble drug paclitaxel (PTX). The density (d_{NP}), R_G (radius of gyration), R_H (hydrodynamic radius), R_G/R_H and R (contrast radius) have been monitored as a function of the amount of drug loaded. The drug entrapment increased the size of PLA and PLGA NPs. On the other hand, it also promoted the shrinkage of PBSBDL NPs. These observations revealed that changes in the inner structure of soft nanoparticles caused by drug loading is not straightforward and it mainly depends on the strength of van der Waals interactions between the polyester core and the probe which is connected to their chemical composition and hydrophobicity. These findings are crucial to understand the key physicochemical parameters involved in the interactions between drug and polymer that affects the final particle structure and influence its loading, release and degradation.

1. Introduction

Polymer chemistry has reached the necessary sophistication to allow the production of macromolecules with accurate control over their structure, composition, and properties. Thanks to the advances in polymer chemistry and polymer colloids, polyester nanoparticles (NPs) have emerged into the biotechnology field and are rapidly heading to the forefront of drug delivery systems, diagnostics and other areas [1–4]. Nowadays, the development of biocompatible polyester-based nanocarriers and their detailed inner characterization is a challenge endeavor in the field of nanotechnology. A substantial volume of literature has been dedicated to the investigation of the effects of particle preparation process on particle properties. It was demonstrated that solvents, emulsifiers and particle composition affect particle size and cargo release. Particular interest is devoted to their biocompatibility and bioabsorbability which has already shown to be very useful in numerous biomedical applications. Moreover, these characteristics can be easily tailored to modify the release, degradation and loading capacity [5,6]. Zhao et al. shown that the drug–carrier compatibility affects drug release in tumour mouse model [7]. It was observed that the drug's hydrophobicity and miscibility with the nanoparticles are two independent key parameters that determine its accumulation in the tumour and their fate on the *in vivo* chemotherapy. Therefore, understanding the relevant physicochemical parameters involved in the interactions between drug and polymer which directly affects the final inner particle structure is crucial towards improvement and tailoring of the drug release, degradation and drug loading capacity.

Recently, the appropriate combination of static and dynamic light scattering (SDLS) has been employed to probe the radius of gyration (R_G) and the hydrodynamic dimension (R_H) of NPs [8]. These techniques can later provide information on the shape and inner structure of scattering objects. Quantitative information on the density of the NPs and draining properties might be also accessed [9] . It is well established that the ratio $\rho = R_G/R_H$ is a characteristic parameter related to the conformation of polymer chains and self-assembled macromolecular objects in solution. For hard-spheres, random coils and rod-like structures ρ-values of 0.775, 1.78, and ≥ 2 have been reported. Furthermore, the ρ-value of spherical objects is dependent on the inner structure and compactness [10] being close to 0.775 for compact spheres, ρ ~ 0.8-0.9 for block copolymer micelles due to solvation phenomena [11] and ρ ~ 1.0 for hollow spheres and vesicles. Additionally, the R_G/R_H ratio of spherical NPs of regular branched polymers or statistical randomly polycondensates are found to be within the range 0.977–1.127 [12–14]. These values are related to the high amounts of water entrapped inside the assemblies which is reported as the soft sphere model [15,16].

In this report, scattering and imaging techniques have been used to probe the structural changes of polymeric nanocarriers due to hydrophobic drug loading and release. The NPs were prepared by using various polyesters and different amounts of the poorly water-soluble drug paclitaxel (PTX). The NPs density (d_{NP}), R_H (DLS), R_G (SLS), R_G/R_H and R (SAXS) have been monitored as a function of the amount of loaded PTX. It is worth mentioning that scattering techniques are powerful tools to probe the inner structure of nanostructured systems. The entrapment of the hydrophobic drug molecule changes the polymeric nanoparticle's matrix leading to the swelling or to the collapse of the entities. These observations are being discussed throughout the manuscript based on polymer architecture, chemical composition, as well as hydrophobicity.

2. Experimental

2.1. Materials

Dimerized fatty acid (DFA) – hydrogenated dilinoleic acid (DLA), trade name Pripol 1009, molecular weight ~570 g mol^{-1}, (C36) (Uniqema BV, The Netherlands), 1,4-butanediol (BD, BASF), succinic acid (Aldrich Chemie), Titanium (IV) isopropoxide (TTIP) (Sigma-Aldrich) acetone (CZ, Merck) and THF (CZ, Merck) were used as received. All other chemicals and solvents were of analytical grade. Solvents were dried and purified by conventional procedures and distilled before use. Paclitaxel (PTX) was purchased from Aurisco, China. Resomer® RG 503H, PLGA, poly(D,L-lactide-*co*-glycolide) 50:50, acid terminated, M_w = 24 000–38 000 g mol^{-1} (T_g = 44 – 48 °C) was purchased from Sigma-Aldrich and used as received. Resomer® R 203H, PLA, poly(D,L-lactide), acid terminated, M_w = 18 000–28 000 gmol^{-1} (T_g = 48–52 °C) was purchased from Sigma Aldrich and used as received. HPLC grade acetonitrile (LiChrosolv®) was purchased from Merck Co. (Darmstadt, Germany). The water used was pre-treated with the Milli-Q® Plus System (Millipore Corporation).

2.2. Synthesis of the PBSBDL, PBS and PBDL

The synthesis of the aliphatic poly[(butylene succinate)-*co*-(butylene dilinoleate)] (PBSBDL) copolyester was performed following the two-steps melt polycondensation (esterification and polycondensation) as previously described [17,18]. Briefly, in a glass reactor it was loaded SA, DLA and BD in molar ratio 1/1/2.2 and the catalyst TTIP (4×10^{-4} mol/mol diacids). The vessel was further evacuated and filled with argon. The reaction mixture was heated at 200 °C and stirred at constant speed (400 rpm). This first step (esterification) was considered complete after the collection of the theoretical amount of H_2O (about 4 h), which was removed from the reaction mixture by distillation and collected in a graduate cylinder. The copolyester was purified by dissolution in chloroform and precipitation in methanol. In order to confirm the positions of the peaks in the ^{13}C NMR spectra for the calculations of the degree of randomness of PBSBDL copolyester the poly(butylene succinate) (PBS) and poly(butylene dilinoleate) (PBDL) homopolyesters were prepared in the same manner as described for PBSBDL.