Colloids and Surfaces A: Physicochem. Eng. Aspects 436 (2013) 714–725

Contents lists available at ScienceDirect

Colloids and Surfaces A: Physicochemical and Engineering Aspects

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

Physicochemical investigations on an engineered lipid–polymer hybrid nanoparticle containing a model hydrophilic active, zidovudine

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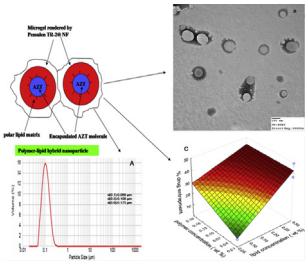
HIGHLIGHTS

- We engineered LPN based on polar lipid and hydrophobically modified polymer.
- LPNs had spherical shape and demonstrated the potential for encapsulation of AZT.
- Molecular interactions were identified among the drug, lipid and the polymer.
- Pemulen polymer was significant to restrict crystallization of the incorporated active.
- Polar lipid and amphiphilic surfactant were significant to modulate drug release.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 16 May 2013
Received in revised form 27 July 2013
Accepted 30 July 2013
Available online 8 August 2013

Keywords:
Lipid–polymer hybrid
Zidovudine
Hydrophilic
Interactions
Amorphization
Recrystallization

ABSTRACT

The objective of this work was to develop an optimized lipid–polymer hybrid nanoparticle (LPN) for zidovudine (AZT), a model hydrophilic active, and further to investigate its crystallization behavior and possible molecular interactions with the carrier during the LPN processing. AZT-LPNs were prepared by melt emulsification-probe sonication technique using a 2^3 factorial design. Transmission electron microscopy (TEM) revealed spherical LPNs with two distinct boundaries representing the drug loaded lipid core surrounded by a polymer. The optimized batch (LPN-2) achieved a size of 175 ± 2.5 nm, drug encapsulation of $49.26 \pm 0.75\%$, and revealed a significant stability for six months. Molecular interactions among the component of LPN were studied by using proton nuclear magnetic resonance (^{1}H NMR), and Fourier transform infrared spectra (FT-IR). The complete amorphization of drug was noted in the melt sample while LPN-2 showed a partial drug recystallization. This was confirmed by the thermal analysis and diffractometry studies. The presence of pemulen polymer was significant to restrict sonication assisted recrystallization of the active. The oscillatory measurement using stress sweep and frequency sweep demonstrated elastic nature of the LPN-2, and was subsequently confirmed through the phase angle (δ°). Fickian diffusion ($n < 0.5$) was identified as drug release mechanism from LPN-2. The partial hydrophilic nature of lipid and the presence of amphiphilic surfactant (Acconon® CO-7) influenced AZT release from LPN. Finally, based on the understanding of molecular interactions, the LPNs made of polar lipid (Cutina® HR) and hydrophobically modified polymer (Pemulen TR-2®) hold the promise to entrap model hydrophilic active, zidovudine, and it is possible to optimize drug release to desired level.

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http://dx.doi.org/10.1016/j.colsurfa.2013.07.044

1. Introduction

Over the last decade, lipid based nanocarriers are viewed as potential tool to encapsulate and deliver variety of pharmaceutical actives [1,2]. The solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are the first and second generation of lipid nanoparticles, respectively. The SLNs are composed of solid lipid or a blend of solid lipids while NLCs contain a mixed lipid core (solid fat and oil). Being generally regarded as safe (GRAS) in status they are able to provide an excellent biocompatibility [2]. Moreover, with the use of NLC carrier it is possible to achieve a high drug loading efficiency [3]. However, owing to the hydrophobic nature of most lipids, it is difficult to entrap and retain water-soluble molecules [4]. Thus, the incorporation of a water-soluble drug in the lipid carrier still poses a challenge. On the other side, with the use of polymer based nanoparticles (PNPs), it is possible to achieve desired size, drug loading, and the release profile [5]. In addition, they can provide better tissue penetrability and stability in biological fluids [6]. Nevertheless, several issues such as, the use of toxic organic solvents in the production process, possible drug leakage from the carrier, and the tedious scale-up processing are frequently associated with PNPs [7]. Thus, both the carriers (lipid and polymer) have the merits and the limitations with respect to their physicochemical and biological properties. Therefore, in this work, we engineered lipid–polymer hybrid nanoparticle (LPN), considering the GRAS nature of lipid and the structural integrity of the polymer. Thus far, the polymers such as polylactic-co-glycolic acid (PLGA) [8,9], hydrolyzed polymer of epoxidized soybean oil (HPESO) [10,11], dextran [12], polyethyleneimine (PEI) [13], protamine sulfate [14], polylactic acid (PLA) [15], and poly-(β-amino ester) [16], have been tried to produce LPNs, with or without organized lipid layer, for the delivery of certain anticancer drugs, antibiotics, and nucleic acids. In this work, we have investigated the use of acrylate/C10–C30 alkyl acrylate cross polymer (Pemulen TR-2®), in the efficient encapsulation of model hydrophilic drug, AZT, in lipid nanocarrier. To prepare the LPNs, at least three main components are required, i.e., the lipid, the polymer, and a drug. The chemical structure of these components is provided in Fig. 1. However, it is important to note that during the processing these components are likely to undergo physicochemical changes resulting in an altered performance of the final product. Thus, to predict final performance of the system it becomes essential to know about the molecular interactions among the main components of LPN. For this purpose, we used proton nuclear magnetic resonance (^{1}H NMR) and Fourier transform infrared spectra (FT-IR). Zidovudine (AZT), an anti HIV molecule, was used as a model hydrophilic drug (water solubility 20.1 mg/mL at RT; log *P*: 0.05). AZT was selected as a model drug as, in an earlier reports, using SLN carrier [17,18] the maximum entrapment achieved was only 27–37%. Furthermore, the current literature reveals no reports on the crystallization behavior of AZT confined to a lipid matrix. It is well known that the change in the crystal lattice of a drug molecule influences its stability, solubility, dissolution rate and bioavailability [19]. Moreover, a high crystallinity of carrier lipid often results in expulsion of an incorporated active, affecting the percent drug entrapment [20]. Therefore, in this work, we investigated crystallization behavior of AZT and the carrier lipid during LPN processing and further identified the factors influencing the crystallization process. For this purpose, we used differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD). Experimental designs and statistical methods are often useful to identify independent formulation variables influencing the responses [21]. In this work, we used a 2^3 (three factors −2 levels) factorial design, to study the various responses as a function of independent variables. In addition, the viscoelastic nature of the developed LPN was investigated through the oscillatory measurements. The developed LPN was further evaluated for its surface morphology, drug release profile, and the stability. Thus, in this work, we designed an optimized LPN for zidovudine (AZT), a model hydrophilic active, and further investigated its crystallization behavior, and possible molecular interactions with the carrier during the processing.

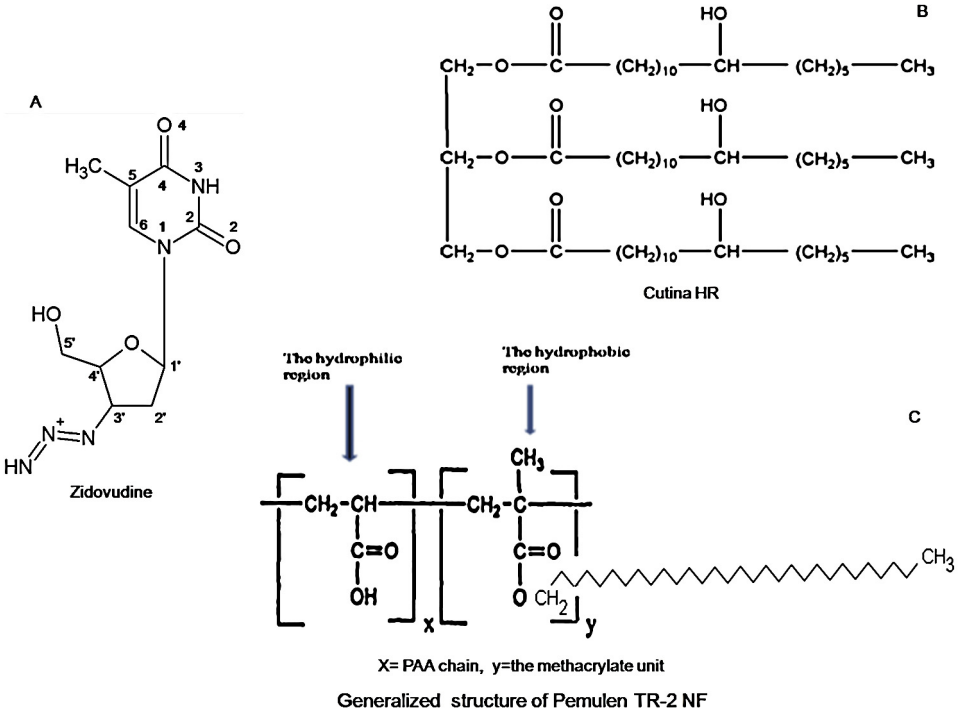

Fig. 1. Chemical structure of drug (A), the solid lipid (B), and the polymer (C).