Production of lipid-polymer hybrid nanoparticles (LPHNPs) for targeted delivery of Roflumilast to lung macrophages

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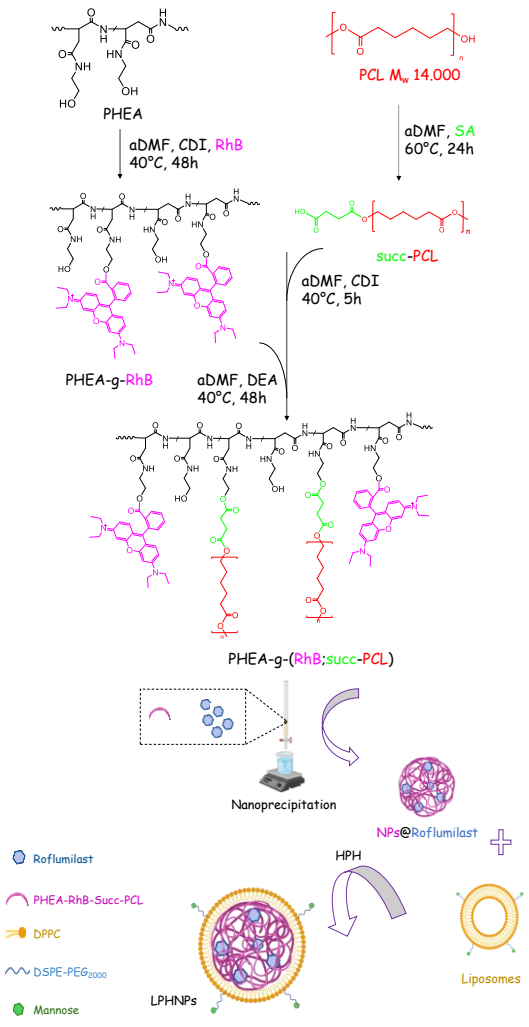
Abstract

Lipid–polymer hybrid nanoparticles (LPHNPs) are innovative core-shell nanostructure recently developed for several biomedical applications, including therapeutics delivery and biomedical imaging. LPHNPs mainly consist of a biodegradable polymeric core, containing drugs, enveloped by a phospholipid layer, which could be decorated on the surface with various targeting ligands. Being a hybrid system between polymeric nanoparticles and liposomes, LPHNPs combine their advantages, such as biocompatibility, controlled particle size, good physical properties, ability to load multiple drugs, excellent storage stability and prolonged drug release profile [1]. The aim of this study was the development of LPHNPs as carriers for pulmonary delivery of Roflumilast, a new selective inhibitor of phosphodiesterase-4 isoenzyme in lung cells for the treatment of chronic obstructive pulmonary disease (COPD). In particular, the polymeric core was constituted of a α,β-poly(N-2-hydroxyethyl)-DL-aspartamide/succinilated polycaprolactone graft copolymer labelled with Rhodamine (PHEA-g-(RhB;succ-PCL)) [2]; the lipid shell was obtained by a mixture between the 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), which is the major component of pulmonary surfactant [3], and the 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-(polyethylene glycol)-Mannose (DSPE-PEG_{2000}-Mannose), in order to obtain LPHNPs targeted to the lung macrophages, which are increased in airways of COPD patients [4].
PHEA-g-(RhB;succ-PCL) was obtained by chemical conjugation of RhB and PCL on PHEA. In particular, alcohol groups of PHEA was first functionalized with RhB to obtain PHEA-RhB with a derivatization degree in RhB (DD_{RhB}) equal to 0.6 mol% . The following step involved the grafting of 2.0 mol% of succinilated PCL on PHEA backbone, to obtain an amphiphilic graft copolymer, highly processable and useful in obtaining polymeric nanoparticles by nanoprecipitation [6]. Roflumilast-loaded LPHNPs were produced by entrapping the drug into the polymeric fluorescent nanoparticles, then the surface covering of these with lipids was done by a two-step method, where preformed PHEA-g-RhB-g-Succ-PCL based nanoparticles were mixed with preformed liposomes by high pressure homogenization (HPH). Empty and Roflumilast-loaded LPHNPs were successfully prepared, with sizes in the nanometer range (~100-150 nm), exhibiting high size uniformity as indicated by polydispersity index (PDI) lower than 0.25, and negative ζ potential. The Drug Loading (DL%) was equal to 1 wt%. The lipid content of DPPC/DSPE-PEG_{2000}-Mannose in LPHNPs was evaluated using ammonium ferrothiocyanate method, and was equal to 60 wt%. XPS and ^{1}H-NMR analyses demonstrated the presence of DSPE-PEG_{2000}-Mannose on the LPHNPs surface. Differential scanning calorimetry (DSC) indicated the entrapment of drug into the hybrid particles in the amorphous state. Besides, Roflumilast-loaded LPHNPs, exhibited an 70% cumulative drug release over 24 h.

Synthesis of PHEA-g-(RhB;succ-PCL) and preparation of LPHNPs



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