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A single-step aerosol process for in-situ surface modification of nanoparticles: Preparation of stable aqueous nanoparticle suspensions

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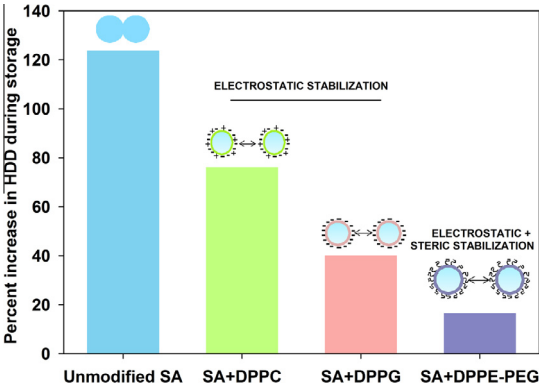
HIGHLIGHTS

- Single-step gas phase process for synthesis and in-situ surface modification of lipid nanoparticles.
- Surface modified nanoparticles exhibited improved suspension stability for an observed period of 30 days.
- Surface modified nanoparticles showed spherical morphology with layered structure and mobility diameters of 130–150 nm.
- Combination of electrostatic and steric effects in surface-modified nanoparticles gave maximum suspension stability.

GRAPHICAL ABSTRACT

In-situ surface modification using an aerosol process, suppressed nanoparticle agglomeration, and consequent hydrodynamic diameter (HDD) increase, in aqueous suspension during 30-day period.



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ABSTRACT

Hypothesis: Surface modification of nanoparticles during aerosol or gas-phase synthesis, followed by direct transfer into liquid media can be used to produce stable water-dispersed nanoparticle suspensions.
Experiment: This work investigates a single-step, aerosol process for in-situ surface-modification of nanoparticles. Previous studies have used a two-step sublimation–condensation mechanism following droplet drying, for surface modification, while the present process uses a liquid precursor containing two solutes, a matrix lipid and a surface modifying agent. A precursor solution in chloroform, of stearic acid lipid, with 4 %w/w of surface-active, physiological molecules [1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-dipalmitoyl-sn-glycero-3-phospho-(1′-rac-glycerol)-sodium salt (DPPG) or 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy (polyethylene glycol) 2000]-ammonium salt (DPPE-PEG)] was processed in an aerosol reactor at a low gas temperatures. The surface modified nanoparticles were characterized for morphology, surface composition and suspension properties.
Findings: Spherical, surface-modified lipid nanoparticles with median mobility diameters in the range of 105–150 nm and unimodal size distributions were obtained. Fourier transform infra-red spectroscopy

Abbreviations: DPPC, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine; DPPG, 1,2-dipalmitoyl-sn-glycero-3-phospho-(1′-rac-glycerol)-sodium salt; DPPE-PEG, 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy (polyethylene glycol) 2000]-ammonium salt; FTIR, Fourier transform infra-red spectroscopy; ATR, attenuated total reflection; WESP, wet electrostatic precipitator; PHAR, pulse heat aerosol reactor; SDS, sodium dodecylsulfate; GSD, geometric standard deviation; TEM, transmission electron microscopy; MMD, median mobility diameter; HDD, hydrodynamic diameter; PDI, polydispersity index; CTAB, cetyltrimethylammonium bromide.

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(FTIR) measurements confirmed the presence of surface-active molecules on external surfaces of modified lipid nanoparticles. Surface modified nanoparticles exhibited improved suspension stability, compared to that of pure lipid nanoparticles for a period of 30 days. Lowest aggregation was observed in DPPE-PEG modified nanoparticles from combined electrostatic and steric effects. The study provides a single-step aerosol method for in-situ surface modification of nanoparticles, using minimal amounts of surface active agents, to make stable, aqueous nanoparticle suspensions.

1. Introduction

Nanoparticles with controlled properties, made of organic, inorganic or magnetic materials, have been explored as promising vehicles for the delivery of drugs to target sites through parenteral routes [1–3]. Lipid nanoparticles used for drug delivery offer physical stability, protection of incorporated labile drugs from degradation and controlled release [3]. Particle size and surface properties strongly influence their suitability for drug targeting to different sites [4]. Drug delivery to target site necessitates formation of a stable dispersion of nanoparticles in water [5]. However, as nanoparticles experience enhanced Brownian diffusion and significant van der Waals interactions, unmodified nanoparticles tend to aggregate in suspension. Such aggregation could lead to specific risks on administration, such as capillary blockage by aggregates after intravenous administration [6]. Suppression of nanoparticle aggregation is assisted by modifying nanoparticle surfaces with polymers or surface-active molecules [5,7]. This is achieved through the creation of a charge or potential barrier, termed electrostatic stabilization, or a physical barrier, termed steric stabilization [8]. Surface modified nanoparticles display improved dispersion characteristics due to reduced inter-particle forces and exhibit higher stability in aqueous dispersions. In addition, modifying nanoparticle surfaces could have other benefits, including reduction in degradation of the core active material during storage.

Two broad classes of methods include *post-synthesis* or *in-situ* surface modification. Post-synthesis methods include adsorption of polymeric dispersants or chemical modification of previously synthesized nanoparticle surfaces using coupling agents or functional groups. However, post-synthesis modification requires collection of nanoparticles as dry powders which is often associated with aggregation during particle collection. In-situ methods involve incorporation of surface-active molecules during particle synthesis itself [7], thus superior for preservation of size distribution properties. Surface modification by either of these methods is often associated with incorporation of large amounts of surfactant molecules posing problems of toxicity.

Major routes used for synthesis of nanoparticles for applications such as drug delivery, bio-sensing and magnetic imaging include colloidal methods [9] and aerosol based methods [10–14]. Aerosol methods provide single-step processing to produce dry, solid nanoparticles, with controlled properties, from biopolymers [13,14] and lipids [10–12]. Production of layered or surface-modified nanoparticles through the aerosol route involved drying of solution droplets generated using coaxial electrospray or a multi-step atomization process. Coaxial dual- and tri-capillary electrospray systems were recently investigated for single-step synthesis of monodisperse biodegradable polymer (poly (lactide co-glycolide)) coated particles containing multiple drugs [15]. Core–shell and tri-layered structures, with different drugs in separate layers demonstrated controlled drug release profiles. However, electrospray systems are reported to be constrained by material choice, which governs conductivity of the solution, as well as a low particle generation rate from the small rates of solution flow through the capillary [16].

In-situ coating of aerosol particles in gas phase is often achieved by physical vapor deposition on inorganic [17] or sub-micron particles [18] employing high temperatures for sublimation of coating material. Simultaneous synthesis and coating of nanoparticles in gas phase has been achieved by a multi-step atomization process. The two-step process consisted of spray drying of air-jet atomized solution droplets containing sodium chloride, polymer Eudragit L100 or drug salbutamol sulfate, followed by condensation of sublimed L-leucine vapor or formation of surface coating by diffusion at high process temperatures of 110–170 °C to initiate sublimation [19–21]. In these studies, L-leucine was used as a surface stabilizer to decrease surface forces between particles to prevent aggregation and improve powder dispersibility or flowability. The sublimation–condensation method limits application to molecules which undergo sublimation, with an additional disadvantage of possible homogenous nucleation of the sublimed molecules [20].

Given constraints in previous methods, there is motivation for attempting surface-modification of nanoparticles using a single-step droplet drying process, based on the aerosol route. Modeling studies have indicated that, during droplet drying, a solute gradient builds up in the drop, whereby the surface solute concentration reaches a critical supersaturation value, initiating crust formation [22–24]. In a two-solute system, containing a surface-active agent, it is of interest to examine whether the expected confinement of surface active molecules in the outermost layer during droplet drying, could result in formation of surface-modified nanoparticles. In the present work, such a process was investigated using a two-solute system, containing thermolabile and non sublimable precursor stearic acid lipid and selected biological surface-active molecules. Attempt was made to synthesize nanoparticles that could be directly collected as aqueous suspensions, for direct pharmaceutical applications and investigations were made of (i) particle properties including size distribution, morphology and surface composition and (ii) suspension stability of surface-modified vis-à-vis pure stearic acid nanoparticles.

2. Experimental methods

2.1. Synthesis of lipid nanoparticles

2.1.1. Precursor solution

Lipid nanoparticles were synthesized at 25 °C (unless otherwise mentioned), using 1.0 mg/mL solution of stearic acid (>95% pure; Sigma Aldrich, Saint Louis, USA) with or without 4 %w/w different surface-active molecules (a) 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC, uncharged phospholipid), (b) 1,2-dipalmitoyl-sn-glycero-3-phospho-(1′-rac-glycerol)-sodium salt (DPPG, negatively charged phospholipid) or (c) 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy (polyethylene glycol) 2000]-ammonium salt (DPPE-PEG, pegylated phospholipid) (Avanti Polar Lipids Inc., Alabaster, AL, USA). In order to study the effect of process parameters on nanoparticle properties, precursor concentrations (0.5, 1.0 and 2.0 mg/mL), synthesis temperature (25 °C and 50 °C) and %w/w of surface active molecule DPPE-PEG (1% and 4%) were varied. Chloroform (>99% pure; Sigma Aldrich, Saint Louis,