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Formation of hydrophilic nanofibers from nanoemulsions through electrospinning

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ABSTRACT

This study presents a method for one step incorporation of lipophilic compounds in hydrophilic nanofibers. By this method nanodroplets of oil and of volatile solvent are entrapped within polymer nanofibers during an electrospinning process. While performing the process with a volatile oil with dissolved lipophilic material, such as the drug celecoxib, nanofiber–nanoparticle composites are formed. The polymer used to form the fibers is a high molecular weight poly(vinyl alcohol) which enables rapid dissolution and release of the incorporated lipophilic material. The resulting celecoxib nanoparticles that are embedded within the nanofiber are amorphous and their average size is in between 21 and 93 nm, thus potentially lead to their increased dissolution rate. The preparation of such a solid matrix containing nanodroplets or nanoparticles may be applied as a fast dissolving delivery system for water insoluble materials.

1. Introduction

For active pharmaceutical ingredients, low aqueous solubility is a major challenge when developing dosage forms for drugs belonging to classes 2 and 4 of the Biopharmaceutical Classification System. Low water solubility leads to low bioavailability which means a low fraction of an administered dose of unchanged drug that reaches the systemic circulation. Bioavailability also depends on other factors such as drug permeability, dissolution rate, first pass metabolism and pre-systemic metabolism. The major factors for low bioavailability are poor solubility and low permeability (Savjani et al., 2012).

More than 40% of NCEs (new chemical entities) developed in the pharmaceutical industry are practically insoluble in water (Merisko-Liversidge and Liversidge, 2008). There are different methods to improve the bioavailability of poorly water soluble compounds such as synthesis of new molecular derivatives, formation of amorphous solid/resin dispersion in a polymer diluent or solubilization of the drug within micelles (Fasinu et al., 2011). The bioavailability can be also significantly improved by size reduction of the drug to the nanometric size range (Horn, 2001).

Reduction of the particle size increases the surface to volume ratio, which causes some materials to have new properties and to increase their interfacial interactions with the medium. The new properties can be both physical and chemical, for example, optical, magnetic, catalytic, thermodynamic and electrochemical (Fasinu et al., 2011; Sanvicens and Marco, 2008). The increased interfacial interaction improves the dissolution rate, saturation solubility and bioavailability. The Noyes–Whitney equation explains the higher solubility of nanometric materials, in which dissolution rate is proportional to the concentration gradient between the bulk concentration of the material in the surrounding liquid and around the particle surface (Dokoumetzidis and Macheras, 2006; Noyes and Whitney, 1897).

Traditional methods to obtain nanoparticles are wet or dry milling (Fasinu et al., 2011) and solvent evaporation from oil-in-water emulsions with nanometric droplets (Rao and Geckeler, 2011). Small droplets can be achieved by using high-energy methods, such as high pressure homogenization or by applying high levels of ultrasound energy. Nanoemulsions can also be formed by the phase inversion temperature (PIT) method which is a low-energy emulsification technique (Rao and McClements, 2011). The principle of the technique is a temperature-induced phase inversion of the emulsion which is stabilized by non-ionic surfactants containing ethoxylated groups (Spernath and Magdassi, 2010b).

Functional components in a form of nanoparticles or nanodroplets can be incorporated into fibers, tubes or networks with

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gel-like or sponge-like characteristics. Of such systems, nanofibers produced from polymers can be an efficient encapsulating matrix due to their high surface-to-volume ratio, from which an encapsulated compound can be readily released (Arecchi et al., 2010).

Electrospinning is a technique for production of nanofibers, which is based on the application of a high-voltage electric field on a solution containing a polymer (Ramakrishna et al., 2005). Under the applied electric field, a polymer jet is ejected from a capillary through which a polymer solution is pumped at a constant rate. The jet is accelerated towards a grounded target and while the solvent evaporates it is deposited thereon (Arecchi et al., 2010). Due to the electric field, charge is induced within the polymer, resulting in charge repulsion within the solution. One of the essential characteristics of an electro-spinnable material is the presence of sufficient chain entanglements that prevent jet breakup because of electrostatic repulsions. If the entanglements are insufficient and the viscosity of the solution is low, electrospray process occurs and leads to particles or droplets formation (Ramakrishna et al., 2005). Additives such as enzymes (Jia et al., 2002), catalysts (Im et al., 2008), carbon nanotubes (Dror et al., 2003) and drugs (Bhardwaj and Kundu, 2010) can be entrapped in entangled electrospinning solutions to form composite nanofibers with various properties.

The electrospinning of nanofibers containing poorly water soluble organic materials has been accomplished by a number of researchers. Most of the works deal with W/O emulsion systems loaded with hydrophilic compounds such as doxorubicin hydrochloride (Xu et al., 2005), bovine serum albumin (Yang et al., 2008a) or lysozyme (Yang et al., 2008b) with lipophilic polymer dissolved in a continuous organic phase (Xu et al., 2005). To the best of our knowledge, few studies have been published that deal with electrospinning of O/W emulsions in nanofibers. One of those studies deals with electrospinning of O/W emulsion with non-volatile oil phase that undergo significant flocculation at higher droplet concentrations (Arecchi et al., 2010). Until recently there was no in situ method for lipophilic nanoparticle formation from nanoemulsion during the electrospinning process. Dvores et al. (2012) reported on nanofibers incorporating nanoparticles fabricated by electrospinning of O/W microemulsion, in which a model lipophilic material was dissolved in the volatile dispersed phase. Microemulsion forms spontaneously under a particular set of composition and environmental conditions (Rao and McClements, 2011; Rosen, 2004) and its stability is affected by additives such as polymers. Therefore it is desirable to simplify the preparation process of a suitable electrospinnable sample. Unlike microemulsions, emulsions stability is less sensitive for presence of additives, usually temperature increase has no immediate effect on the structure and dilution of the sample with the continuous phase does not results in modification of the droplet size or phase separation (Anton and Vandamme, 2011).

In this study we describe a novel simple one-step process to obtain hydrophilic nanofibers with embedded emulsion nanodroplets or nanoparticles. The process is based on electrospinning an-oil-in water nanoemulsion, in which poly(vinyl alcohol) (PVA) is dissolved in the continuous phase of the nanoemulsion. PVA was chosen for the electrospinnable solution because of its non-toxicity and biocompatibility (Shao et al., 2003) in addition its high molecular weight fulfills the requirement of electrospinnable material (Koski et al., 2004; Yao et al., 2003). The nanoemulsions are prepared by a phase inversion method. The nanodroplets are either made of non-volatile oil phase in which lipophilic materials are dissolved, or made of a volatile solvent with a dissolved lipophilic material. In the latter, the formation of the nanofibers is accompanied by the evaporation of the emulsion's droplets. The instant evaporation of all the liquid components of the emulsion generates solid nanoparticles that are embedded within the nanofiber. The rapid potential dissolution of the hydrophilic nanofibers in an aqueous medium would enable immediate dispersion and dissolution of the lipophilic nanoparticles, and therefore can serve as a useful delivery system in fields such as pharmaceutics, food and agriculture.

2. Materials and methods

2.1. Materials

Poly(vinyl alcohol) (PVA) (MW = 205,000, degree of hydrolysis = 86.7–88.7), Brij O10 (polyethylene glycol oleyl ether), Tween 80 (polyoxyethylene (20) sorbitan monooleate), Span 80 (sorbitan oleate), Nile Red and *n*-butyl acetate (*n*BuAc) (min. 99.5 %) were obtained from Sigma–Aldrich (Israel). Isohexadecane (Arlamol HD, Lanxess), retinyl palmitate (DSM), sodium chloride (min. 99.6%, J.T. Baker) and all the other materials were used without further purification. Celecoxib was a gift from Teva Pharmaceutical Industries (Israel). All solutions were prepared with deionized water.

2.2. Non-volatile nanoemulsion preparation by phase inversion temperature (PIT) method

Retinyl palmitate 4.2 wt% was dissolved in isohexadecane, and in some experiments, a fluorescent probe, Nile Red was also dissolved (0.002 wt%), prior to emulsification. The oil phase was added dropwise to the aqueous phase (10 mM NaCl and 7 wt% Brij O10). A crude O/W emulsion with 20 wt% dispersed phase was prepared by mixing the oil and the aqueous phase using magnetic stirrer for 15 min. Then it was heated above the PIT, the temperature at which emulsion inversion occurs and a W/O emulsion was obtained, followed by rapid cooling in an ice bath, resulting in an O/W nanoemulsion. The phase inversion point was detected by the sudden drop in conductivity (Oyster, Extech). The PIT was taken as the average value of the temperature at which the conductivity was the highest and the lowest (Spernath and Magdassi, 2010a).

2.3. Volatile nanoemulsion preparation

The nanoemulsion contained 20 wt% *n*-butyl acetate, which was chosen as the volatile dispersed phase because its evaporation rate is higher than the evaporation rate of water, it has a low water solubility (0.83 wt% at 25 °C) and a low toxicity (O'Neil, 2006). Mixtures of two surfactants, Tween 80 and Span 80 (4 wt% in total) at different ratios, were used to form the nanoemulsions. The initial emulsion was prepared by mixing the two phases with a magnetic stirrer for 15 min followed by sonication with a probe sonicator (JY88-2N, MRC) with pulse every 2 s, at 300 W and 5 min total emulsification duration. The optimal ratio between the two surfactants was found by measuring the droplets size.

After the optimization of the nanoemulsion's composition, the effect on droplet size distribution of an additional preparation method was studied. Crude emulsions were obtained with a homogenizer (Ultra Turrax T-25 Basic, IKA-Werke) by adding the oil phase to the aqueous phase while stirring 10 min at 10,000 rpm. To decrease the emulsion droplet size to the nanometric range, the emulsion was passed through a high pressure homogenizer (110L, Microfluidics) for several cycles until an optimal droplet size was reached. A fluorescent marker, Nile Red was added as mentioned in Section 2.2.

For preparing nanofibers with embedded drug nanoparticles we prepared nanoemulsions incorporating a lipophilic drug, celecoxib (aqueous solubility 3–7 μg/ml at pH 7 and 40 °C) by