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Electrosprayed poly(butylene succinate) microspheres loaded with indole derivatives: A system with anticancer activity

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ABSTRACT

Electrospraying of poly(butylene succinate) and its mixture with different indole derivatives was successfully performed using chloroform as solvent and relatively low flow rates and concentrations. Morphology of particles (size, diameter distribution and surface texture) and encapsulation efficiency were dependent on the loaded drug and specifically on the type of substituent (methyl or phenyl) and its position in the indole core. In general, particles showed a raisin-like morphology caused by the shell collapsing of the resulting structurally weak microspheres. Accumulation of electrosprayed particles gave rise to consistent mats and they had a more hydrophobic surface than that determined for smooth films. The increase of hydrophobicity was mainly dependent on the porosity and the hydrophobic nature of the incorporated drugs. Indole derivatives were hardly delivered in a standard phosphate saline buffer due to their scarce solubility in aqueous media but the addition of ethanol caused a drastic change in the release behavior. This was generally characterized by a fast burst effect and followed by the establishment of an equilibrium condition that was dependent on the indole derivative. However, a clearly different behavior was found when the indole was unable to form hydrogen bonds (e.g. 1-methylindole) since in this case a slow and sustained release was characteristic. Microspheres loaded with indole derivatives showed a high antiproliferative activity that was dependent on encapsulation efficiency and the type of loaded drug. The best results were specifically attained for the indole with an aromatic substituent. Interestingly significant differences were found between cancer and immortalized cells, a feature that points out the potential use of such systems for cancer prevention and treatment.

1. Introduction

Electrospinning and electrospraying are electrohydrodynamic atomization techniques that are widely employed in nanotechnology. These top-down physical methods can lead to materials at the nano- or microscale level through the interaction between electrical energy and processed fluids [1,2] without involving a previous energy-transfer process (e.g. ultrasounds or microwaves) [3]. Electrical energy from electrospinning allows the removal of organic solvents and the production of polymer nanofibers or even nanoparticles suitable for drug delivery applications [4–6].

Electrospinning techniques are based on the application of a high voltage between the tip of a polymeric solution container and a counter electrode located at a collector. The solution drop at the tip is deformed by the electrical field, and when

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the electrostatic forces of repulsion overcome the droplet surface tension, a charged jet ejects and deforms uniaxially through the electric field toward the collector. The microfluid jet is quickly dried (often in the order of 10^{-2} s) producing continuous nanosized fibers [7,8]. Loading of active substances such as drugs can also be easily achieved (e.g. by simple inclusion of the drug into the electrospinning polymeric solution) and furthermore the loaded nanofibers may exhibit excellent performance in enhancing the dissolution rates of poorly-water soluble drugs. Therefore, electrospinning becomes a useful tool for generating solid dispersions of poorly water-soluble drugs [9].

The electrospray technique is derived from electrospinning. Electrosprayed particles are produced when the formed liquid jet undulates and breaks up into small electrically charged droplets which repel each other and form a dispersed shower downwards to the collector. A progressive decrease in droplet diameter can be derived from the continuous evaporation of the solvent. Nowadays, electrospraying has grown in popularity because of its simplicity and ability to produce particles with a mean diameter that can be varied between hundreds of micrometers to tens of nanometers [10]. Therefore, electrospraying has been utilized to produce materials with a wide range of applications in areas as diverse as pharmaceutical, ceramics, cosmetics and food industries but, especially, it appears useful for biomedical applications such as drug delivery [11].

A great number of synthetic and natural polymers have been successfully formulated into microspheres by means of electrospraying [12–14]. Despite the simplicity of the process, operational parameters must be experimentally found for each polymer in order to attain the desired particle size, morphology and size distribution.

Biodegradable and biocompatible polymers have received particular attention as drug delivery systems, being in this case highly interesting to obtain particles with homogeneous sizes for a good control of the drug release rate. Physicochemical properties of the selected polymer determine the interactions with the active compound and influence the drug encapsulation/entrapment process as well as the drug release kinetics. Polylactides have been widely employed for encapsulation of therapeutic molecules due to their biodegradability and biocompatibility. Those requisites can also be found with poly(alkylen dicarboxylate)s, being probably poly(butylene succinate) (PBS, Fig. 1) the most significant polymer of this family due to its unusual combination of good properties (e.g. thermal and mechanical) as well as the relatively high molecular weight that could be obtained through the polycondensation reaction [15].

Indole derivatives occur widely in natural products, existing in different kinds of plants, animals and marine organisms [16]. The indole core is a near-ubiquitous component of biologically active natural products. For example, among the microorganisms in some bacteria, indole is used as a cell-signaling molecule in both intra- and inter-species communication (process termed quorum sensing) [17,18]. The indole core is also well known as one of the most important "scaffolds" for drug discovery, a term first introduced by Evans and co-workers to define scaffolds which are capable of serving as the ligand for a diverse array of receptors [19–21]. The indole core has been deemed as an important moiety found in many pharmacologically active compounds (Table 1). These possess certain biological features such as anticancer effectiveness [34–41] and antiviral activity [42]. Furthermore, indole derivatives have the unique property of mimicking the structure of peptides and reversibly bind enzymes [43,44]. There is an amazing number of approved indole containing drugs in the market as well as compounds currently going through different clinical phases or registration states. In fact, seven indole-containing commercial drugs can be found between the Top-200 Best Selling Drugs by US Retail Sales in 2012 [45]. The most relevant is Cialis, an approved drug for the treatment of men's erectile dysfunction and the signs and symptoms of benign prostatic hyperplasia [46,47].

In summary, the broad spectrum and the important physiological activities of indole-derivatives make highly desirable the fabrication of loaded micro/nanoparticles with them for their use in several biomedical applications. Herein, we report an efficient and simple strategy to prepare polybutylene succinate (PBS) microspheres loaded with indole and

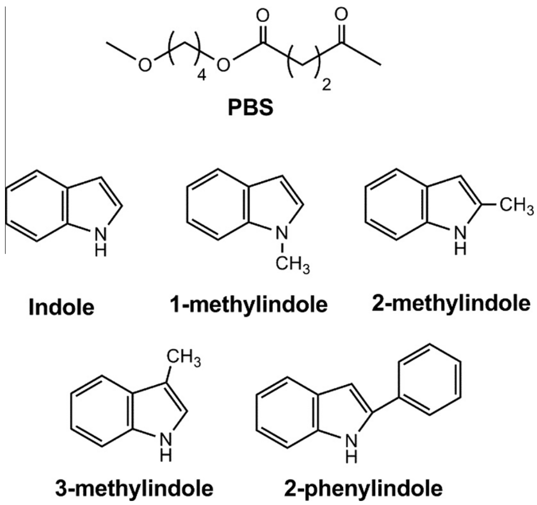

Fig. 1. Chemical structures of poly(butylene succinate) (PBS) and the selected indole derivatives.