Poster

Nanotechnology-based new systems in drug delivery

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Introduction

At present 95% of all new potential therapeutics have poor pharmacokinetics and biopharmaceutical properties. Nanotechnology plays an important role in therapies by lowering doses required for efficiency as well as increasing the therapeutic indices and safety profiles of newer therapeutics. Here, there are reported three experimental examples of delivery nano-systems based on a biodegradable polymer, poly(D,L-lactide-*co*-glycolide) (PLGA) or natural phospholipids obtained by two different technologies which are briefly described below.

Materials and Methods

Technologies

Two mechanical technologies were employed to produce nanoparticles containing different active molecules.

Flow Focusing (FF). This is a simple atomization technique based on the combination of a specific geometry and hydrodynamic forces. FF provides a remarkable accuracy in size, narrow size dispersion, and feasibility [1-4]. The phenomenon is characterized by the presence of a steady micro-jet which is "sucked" through a small orifice, and eventually breaks up into droplets of well-defined size and structure (Figure 1a).

High pressure homogenization (HPH). A fluid mechanical process that involves the subdivision of particles or droplets into micron sizes. The process occurs in a special homogenizing valve creating conditions of high turbulence and shear, combined with compression, acceleration, pressure drop, and impact which cause the disintegration of particles and dispersion throughout the product (Figure 1b).

Production of nanosystems. Experimental examples:

1. PLGA-Gemcitabine nanoparticles for oral administration. Gemcitabine is a water soluble anticancer drug with very short plasma half-life. To obtain the nanoparticles, FF technology was used. In this case, a primary o/w emulsion was carried out by dispersing a gemcitabine aqueous solution into a PLGA solution in ethyl acetate. This o/w emulsion was sprayed inside a hot chamber. The resulting solid polymeric particles were collected at the bottom of the chamber.
2. PLGA- Δ^9-THC (Δ^9-tetrahydrocannabinol) or CB13 nanoparticles for oral administration. THC and its derivates are small oily molecules, recently accepted for neurology pain treatment. Nanoparticulated systems containing THC can avoid the drug accumulation on adipose tissue, among other advantages. In this case, drug and polymer were co-dissolved in ethyl acetate and used as focused fluid in a simple FF nozzle. Particles were produced inside a polyvinyl alcohol (PVA) bath under continuous agitation, and then particles were centrifuged and washed three times.
3. Lipid Nanoparticles (LN) for topical administration. These kinds of particles, among other advantages, allow achieved high levels of hydration by increasing the occlusion grade [5]. We prepared vitamin E loaded nanoparticles based on a mixture of fatty alcohols and a surfactant (Mygliol 813; Compritol ATO; Monostearin, Span 60, 0.25%) using HPH equipment (1 cycle, 1000 bar, 75 ºC) (Panda 2K, Niro Soavi).

Characterization methods: *Particulate size.* Particles diameters were measured by photon correlation scanning (PCS) using a Partica LA-950V2 analyzer (Horiba). *Zeta potential* (ς) measurements were carried out in using a Malvern Zetasizer (UK) (PBS 7.4, 25ºC). *Drug content* was determined by HPLC on a Hitachi LaChrom® (D-7000) Series HPLC system. *Scanning electron microscopy* (SEM) was used to evaluate nanoparticles aspect and morphology.

Results and Discussion

Several methods to obtain drug loaded-nanoparticles using two different technologies (FF, HPH) have been developed. Drugs having radical different physicochemical and biopharmaceutical properties have been assayed. By FF (PLGA nanoparticles), particles around 1 µm in diameter and narrow size distribution have been obtained (CV <= 10%). Zeta potential for PLGA nanoparticles were lightly

negative (ς ~ - 20 mV) which points out a favourable nanoparticles up take on Peyer´s patch. Lipid nanoparticles (230 - 280 nm in diameter, Figure 2b,c) were obtained in two different internal structures: solid (SLN, perfect matrix) and nanostructured lipid carrier (NLC, imperfect matrix) according to the assayed formulations.

Conclusions

The present study shows that Flow Focusing and HPH are suitable technologies to produce solid polymeric and lipid nanoparticles with uniform shape, mean size and size distribution.
We have established the possibility to obtain PLGA nanoparticles containing water and no-water soluble drugs with suitable properties for oral administration. Lipid nanoparticles for topical administration have been also produced with real small sizes allowing high levels of occlusion and hydration. FF technology is characterized by a high control on particle diameter and can also predict final particle diameter [1]. HPH can produce particles at very high rate (10L/h) in a continuous manner keeping constant high temperatures required for lipid formulations production.

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Figures:

Figure 1. Technologies employed to produce drug-loaded nanoparticles: (a) Simple FF nozzle [6]; (b) scheme of the main pieces of HPH equipment

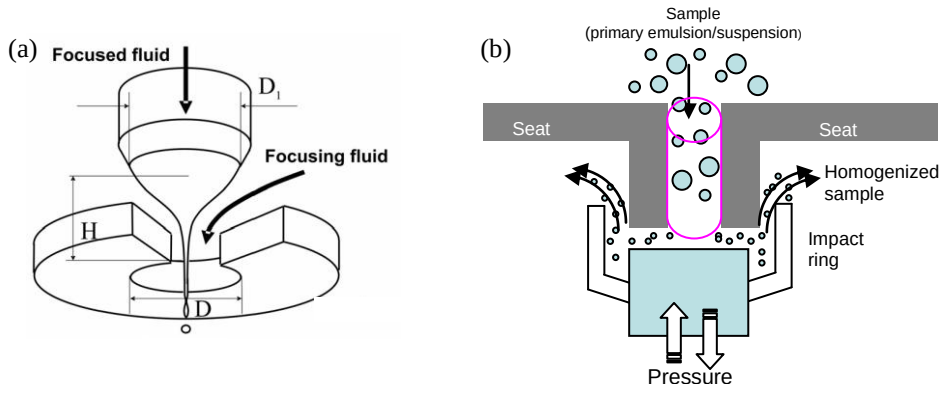
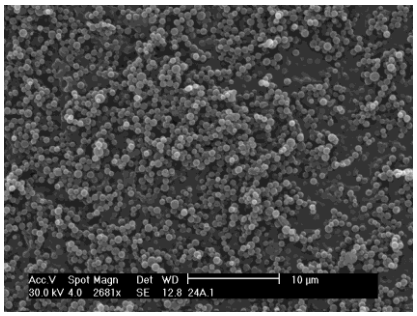


Figure 2. (a) SEM image of PLGA-Gemcitabine nanoparticles; (b) Mean diameter for SLN and NLC produced by HPH and (c) Typical size distribution for lipid nanoparticles obtained by HPH

(a)



(b)

	D_{mean} ± SD (nm)	polydispersity index
SLN	288,0 ± 2,1	0,096 ± 0,019
NLC	234,4 ± 2,9	0,208 ±0,008

(c)