Colloids and Surfaces B: Biointerfaces 90 (2012) 8–15

Contents lists available at SciVerse ScienceDirect

Colloids and Surfaces B: Biointerfaces

journal homepage: www.elsevier.com/locate/colsurfb

Nano and microparticle engineering of water insoluble drugs using a novel spray-drying process

Nina Schafroth[b], Cordin Arpagaus[b], Umesh Y. Jadhav[a], Sushil Makne[a], Dennis Douroumis[a,*]

[a] University of Greenwich, Medway School of Science, Medway Campus, Chatham Maritime, ME4 4TB, Kent, United Kingdom
[b] BÜCHI Labortechnik AG, Meierseggstrasse 40, 9230 Flawil, Switzerland

ARTICLE INFO

Article history:
Received 17 June 2011
Received in revised form
10 September 2011
Accepted 13 September 2011
Available online 4 October 2011

Keywords:
Spray-drying
Nanoparticles
Microparticles
Biodegradable polymers
Encapsulation

ABSTRACT

In the current study nano and microparticle engineering of water insoluble drugs was conducted using a novel piezoelectric spray-drying approach. Cyclosporin A (CyA) and dexamethasone (DEX) were encapsulated in biodegradable poly(D,L-lactide-co-glycolide) (PLGA) grades of different molecular weights. Spray-drying studies carried out with the Nano Spray Dryer B-90 employed with piezoelectric driven actuator. The processing parameters including inlet temperature, spray mesh diameter, sample flow rate, spray rate, applied pressure and sample concentration were examined in order to optimize the particle size and the obtained yield. The process parameters and the solute concentration showed a profound effect on the particle engineering and the obtained product yield. The produced powder presented consistent and reproducible spherical particles with narrow particle size distribution. Cyclosporin was found to be molecularly dispersed while dexamethasone was in crystalline state within the PLGA nanoparticles. Further evaluation revealed excellent drug loading, encapsulation efficiency and production yield. In vitro studies demonstrated sustained release patterns for the active substances. This novel spray-drying process proved to be efficient for nano and microparticle engineering of water insoluble active substances.

1. Introduction

In the last decade nanoparticle engineering of water insoluble active substances has attracted increased attention [1]. It is estimated that about 40% of active substances during formulation development by the pharmaceutical industry are poorly water soluble [2–4]. Several strategies have been employed to formulate drug nanoparticles such as nano-emulsions [5], nanosuspensions [6], solid lipid nanoparticles [7], liposomes [8], micelles [9] or inorganic nanoparticles [10]. The development of nanoparticles is of critical importance for actives that are classified by the Biopharmaceutical Classification System (BCS) as a Class II.

Nano and microparticle engineering via spray-drying has been as introduced as an attractive manufacturing process in the pharmaceutical industry due to its wide applicability [11]. For instance, spray-drying has been used to increase drug solubility and bioavailability of active substances, modified release, pulmonary delivery of proteins or vaccines or for processing of viable organisms [12,13]. Spray-drying is the transformation of a liquid or a dispersion feed from the liquid state into a powdered material by spraying the feed into a hot drying medium [12]. A typical spray-drying process consists of four steps that include atomization of the liquid stream, vaporization/drying of the liquid stream through the drying gas, particle formation and subsequently particle separation and collection. Recent advantages in the spray-drying led to new innovative technologies such as the Nano Spray Dryer B-90 developed by Büchi Labotechnik AG. The unique feature of this technology is the droplet generation through a piezoelectric driven actuator that operates at a specific ultrasonic frequency and thus creating a mist of droplets with extremely ultra-fine particle size. The dried particles are electrostatically charged and collected at the collecting electrode surface with minimal particle wastages and high formulation yields.

In a recent publication Mundargy et al. [14] highlighted the use of spray-drying as an effective technology to deliver macromolecular active substances encapsulated in poly(D,L-lactide-co-glycolide) (PLGA) and its derivatives. However, the implementation of water-in oil-in water (w/o/w) emulsification or phase separation techniques is a prerequisite before the application of the spray-drying process. These additional processing steps render proteins or peptides susceptible to denaturation, aggregation, oxidation and cleavage. In the case of water insoluble actives or peptidic substances they might also result insufficient solubility increase and low encapsulation efficiency [15]. Furthermore, the incorporation of stabilizers or emulsifiers such poly(vinyl alcohol) or

* Corresponding author.
E-mail addresses: d.douroumis@gre.ac.uk, dennis_douroumis@yahoo.com (D. Douroumis).

0927-7765/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.colsurfb.2011.09.038

amphiphilic surfactants, which are difficult to remove, imparts additional drawbacks. A surfactant free processing technology will minimize the preparation efforts, prevent the side-effects from the surface located surfactant and polymer degradation.

Recently, Li et al. [16] investigate the advantages and limitation of the new spray-drying process and emphasized the particle size, distribution, homogeneity, morphology, formulation yields of various polymeric materials and the different experimental conditions to produce drug encapsulated nanoparticles or drug crystals. The major advantages of this approach are the processing of small volumes, the high yields and the small particles that can be obtained. In the current study we optimized the processing parameters of the new spray-dryer to produce PLGA nanoparticles with cyclosporine A (CyA) or dexamethasone (DMX) encapsulated within the polymer core. The alteration of the processing parameters has a great effect on the obtained particle size and production yield. Furthermore, we explored the effect of the process on the solid state properties and release profiles of the engineered nanoparticles. PLGA polymers are commercially available approved by the US Food and Drug Adiministration (US FDA) for human use [17] at various molecular weights (MW) and lactide/glycolide ratios. They are mainly used for controlled release of actives and various commercial products are already in the market. The study revealed that the polymer molecular weight, degradation characteristics and the drug–polymer interactions play a key role on the solid-state solubility, encapsulation efficiency and release patterns of the produced nanoparticles. Nevertheless, spray-drying has been used in several occasions for the development of PLGA nano or microparticles [17–22].

2. Materials and methods

2.1. Materials

Cyclosporine CyA was kindly donated by Novartis Pharma AG (Basel Switzerland). Dexamethasone (DEX) and poly(DL-lactide-co-glycolide) (PLGA) [lactide:glycolide 50:50, 40–70 kDa, 15 kDa and lactide:glycolide 85:15, 50–75 kDa] grades were purchased from Sigma–Aldrich (UK). All the other chemicals and solvents were analytical and high performance liquid chromatography grade.

2.2. Spray-drying process

Preparation of nanoparticles was carried out by the Nano Spray Dryer B-90 (Büchi, Switzerland). To obtain drug loaded nanoparticles 100 mg of either CyA or DEX and 500 mg of PLGA of different lactide:gylcolide ratio and molecular weights were accurately weighted and dissolved in 0.5–2% solid content of a dichloromethane/ethanol (70/30%, v/v) organic solution and stirred to produce a clear solution. For the purposes of the study spray meshes of 4.0 and 5.5 μm were used with 60 Hz ultrasonic frequency for the actuator. The rest of the processing parameters varied according to Table 1. The produced powders were collect and weighted to estimate the product yield.

The Nano Spray Dryer B-90 apparatus was connected to a cooling unit, the Inert Loop B-295, for safe operation of solvents in a closed-mode configuration. Nitrogen was used as an inert gas, at 1.5 bars, to prevent an explosive gas mixture. The CO_2 gas supply was used to build the electrical field for separation of the particles at 1.5 bars.

2.3. Operation principles of the Nano Spray Dryer B-90

The operational principle of the Nano Spray Dryer B-90 (Fig. 1) is based on a piezoelectric crystal driven actuator, vibrating a thin,

Table 1
Spray-drying process parameters of the Nano Spray-Dryer B-90 ($n = 3$).

No.	Sample-Concentration (%)		Inlet temp. (°C)	Outlet temp. (°C)	Spray mesh (μm)	Spray rate[a] (%)	Pressure (mbar)	Gas flow rate (l/min)	Head temp. (°C)	Sample flow rate (ml/h)	Size (μm)	Yield (%)
1	CyA/PLGA (50:50, 40–70 kDa)	1.0	32	30	5.5	100	36	102	36	16	2.23 ± 0.63	20.05
2	DEX/PLGA (50:50, 40–75 kDa)	2.0	32	31	5.5	50	44	129	43	10	0.95 ± 0.43	52.0
3	DEX/PLGA (50:50, 40–70 kDa)	1.0	30	31–32	5.5	98	40	111	39	12	1.65 ± 0.45	32.4
4	CyA/PLGA (50:50, 40–75 kDa)	2.0	30	29	4.0	50	51	120	39	12	1.60 ± 0.65	36.0
5	DEX/PLGA (50:50, 15 kDa)	1.0	32	30	5.5	75	44	129	43	10	1.27 ± 0.38	54.24
6	CyA/PLGA (50:50, 15 kDa)	1.0	29	29	5.5	90	46	110	45	12	0.95 ± 0.52	51.13
7	DEX/PLGA (85:15, –70 kDa)	2.0	30	28	5.5	70	47	132	37	10	0.90 ± 0.47	50.0
8	CyA/PLGA (85:15, –70 kDa)	1.0	32	29	5.5	90	44	110	45	12	1.78 ± 0.64	55.5
9	CyA/PLGA (85:15, –70 kDa)	0.5	32	29	5.5	50	44	110	45	12	1.61 ± 0.55	33.2

[a]Maximum flow rates of 4.0 μm and 5.5 μm mesh sizes are 20 ml/h and 60 ml/h respectively.