Powder Technology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Powder Technology

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

Polymeric microparticles containing indomethacin for inhalatory administration

Nazareth Eliana Ceschan [a,b], Verónica Bucalá [a,b], María Verónica Ramírez-Rigo [a,c,*]

[a] Planta Piloto de Ingeniería Química (PLAPIQUI), CONICET — Universidad Nacional del Sur (UNS), Camino La Carrindanga Km 7, (8000) Bahía Blanca, Argentina
[b] Departamento de Ingeniería Química, UNS, Avenida Alem 1253, (8000) Bahía Blanca, Argentina
[c] Departamento de Biología, Bioquímica y Farmacia, UNS, San Juan 670, (8000) Bahía Blanca, Argentina

ARTICLE INFO

Available online xxxx

Keywords:
Polyelectrolyte–drug complexes
Pulmonary route
Non-steroidal antiinflammatory drug
Spray drying
Polylysine
Particle engineering

ABSTRACT

Indomethacin (IN) is a non-steroidal antiinflammatory drug. It reduces pain and inflammation in rheumatoid arthritis but its use is associated with high incidence of undesirable gastrointestinal side effects. In addition, its low solubility in water limits its oral bioavailability. In this work, microparticles based on an IN–polylysine (PL) complex were obtained by spray drying. The system is intended to deliver the drug through the inhalatory route for both local and systemic treatments. Several formulations, varying the relative composition IN/PL–dextrin (DX) and the total solid content of the feed solutions, were tested. The process performance (yield, air outlet temperature), product properties (IN load efficiency, moisture content, crystallinity, glass transition temperature, density, morphology and particle size distribution), the IN–polylysine ionic interaction (assessed by FT-infrared spectroscopy, powder X-ray diffraction and thermal analysis), and in vitro IN release were studied. Powders exhibited high load efficiencies and low moisture contents, and remained in the amorphous state after nine months of storage. The particle systems with 50% of the polylysine amino groups neutralized by IN were the more attractive ones for pulmonary treatment, since they were easily processed using a homogeneous aqueous feed, had relatively high IN contents and high cumulative fraction of respirable particles.

1. Introduction

Non-steroidal antiinflammatory drugs (NSAIDs) are a family of active ingredients that shares pharmacological applications and side effects. In general, they have analgesic, antiinflammatory and antipyretic properties [1]. The World Health Organization developed a 3-step conceptual model to guide the pain management, suggesting that the NSAIDs should be the first option in chronic and acute therapies [2]. Common side effects of NSAIDs are gastrointestinal lesions, the most frequently ones are minor and well tolerated. However, the NSAIDs can also cause erosions and gastric and duodenal ulcers. Less often, NSAIDs cause kidney problems, hypersensitivity and hematologic reactions [1]. Due to gastrointestinal complications, NSAIDs are the second pharmacological group more recurrently involved in adverse reactions to drugs. From the all side effects treated in hospitals, 20% are because of NSAIDs. Between 1 and 3% of people who consume these medicines for at least one year develop adverse drug reactions, and 5–10% of them suffer gastric ulcers [3].

Inhalatory route is an attractive non-invasive alternative route for the delivery of active ingredients in local and systemic treatments [4]. Currently the global market for this type of drug delivery is growing rapidly. Both nasal and pulmonary administration allows improving bioavailability, because an extensive surface area and an epithelial layer highly vascularized are available for absorption. Also, the inhalatory administration allows avoiding the hepatic first-pass metabolism [4]. Particularly, inhalatory route is an interesting alternative for gastrolesive active ingredients like NSAIDs. Within this drug group, nasal and pulmonary administration of ketoprofen, meloxicam and ibuprofen was previously addressed [5–7]. The developed formulations (aerosols and dry powders) were designed to avoid the oral administration of NSAIDs and to treat local illnesses of the upper respiratory tract.

Other drug candidate for inhalatory administration is Indomethacin (IN), a NSAID derived from indoleacetic acid (Fig. 1a). It reduces pain and inflammation in osteoarthritis, rheumatoid arthritis and tendinitis [8]. Although it is a very effective drug, it presents low oral bioavailability due to its poor aqueous solubility [8] when it is administered as immediate release solid oral dosage forms. According to the Biopharmaceutics Classification System, IN is categorized as class II drug (low solubility and high oral permeability [8]). Consequently, important efforts were done to improve IN dissolution rate for oral applications. Among others, particle size reduction, usage of IN at its amorphous state and preparation

* Corresponding author at: Planta Piloto de Ingeniería Química (PLAPIQUI), CONICET — Universidad Nacional del Sur (UNS), Camino La Carrindanga Km 7, (8000) Bahía Blanca, Argentina. Tel.: +54 291 486 1700x265; fax: +54 291 486 1600.
E-mail address: vrrigo@plapiqui.edu.ar (M.V. Ramírez-Rigo).

http://dx.doi.org/10.1016/j.powtec.2015.02.001
0032-5910/

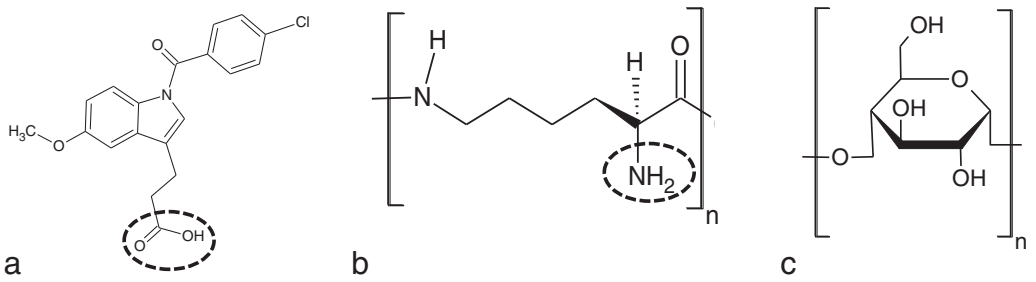

Fig. 1. Structural formula of a) indomethacin (IN) b) polylysine (PL) and c) dextrin (DX, only the α 1, 4 link is represented). Circles highlight the acidic and basic groups of IN and PL that participate in the complex formation, respectively.

of aqueous soluble inclusion complexes carrying the drug [9,10]. In particular, the amorphous state of IN was extensively studied; however this state is unstable, limiting its application [10]. Regarding the IN particle size reduction, it was reported a size limit for which further size reduction did not improve the dissolution rate and moreover particle agglomeration can be observed [11]. Inclusion complexes have the disadvantages of a limited drug load efficiency [9].

Moreover, its use is limited because of the high incidence of gastrointestinal side effects [1,8]. The IN inhibits the secretion of prostaglandins that protect gastric tissues and has relative large residence times in contact with the stomach mucosa because at acid pH this drug is trapped and accumulated within cells [1]. The most frequently gastrointestinal complications are dyspepsia, hyperacidity, nausea, vomiting and epigastric pain, ulcers and erosions [1]. For this reason, alternative systemic administration routes were explored to avoid the acute local pH-dependent [12,13]. Among them, the inhalatory route was explored. Huang et al. [14] studied in vivo the IN nasal administration delivered as a solution (with sodium bicarbonate) and demonstrated that IN has an adequate absorption through the nasal mucosa and can reach the systemic circulation in a similar way than when it is orally administered. Based on this result, Karasulu et al. [15] also studied in vivo the IN nasal administration using emulsions with different excipients to enhance the drug permeation and thus the bioavailability. Although these previous contributions are interesting, the IN pulmonary administration would allow both systemic and local treatments of patients with rheumatoid arthritis-associated lung disease [16]. In this sense, Onischuk et al. [17] explored the effectiveness of pulmonary administration of pure IN in mice proving that lower doses of IN are necessary to achieve the joint anti-inflammatory action compared to oral administration. However, the dose deposited in the lung is low.

To deliver this drug to the alveolus, it is necessary to design a formulation capable to reach the lung respiratory regions. The current tendency of inhalable systems is oriented to dry powder inhalers, which have competitive advantages in terms of stability and efficiency over nebulization systems or metered dose inhalers [18]. However, for dry powder inhalers a rational design of the particulate system is required. The characteristics of the material (shape, size, density, porosity, surface charge, chemical composition, among others) strongly affect the particles' aerosolization and deposition, as well as the drug release and residence time at the action or absorption site [19]. Therefore, the powder properties modify significantly the biopharmaceutical performance of the formulation [19].

Spray drying (SD) is a technology for producing particulate systems with controlled quality by a suitable selection of the fluid feed composition and process operating conditions [19]. This process is currently selected to develop inhalable particles because it is a scalable continuous technology, able to process a variety of liquid feeds (solutions, dispersions and emulsions) based on substances of different natures [19,20].

To overcome IN physicochemical and biopharmaceutical problems, an adequate formulation design of feed fluid is necessary to enhance the product properties. In this work the preparation of inhalable particulate systems based on ionic complexes between IN and a polyelectrolyte is proposed to improve the IN bioavailability and to avoid the gastrointestinal adverse side effects of this drug. For the inhalatory route, epsilon-polylysine (PL) is an interesting polyelectrolyte (polymer with amino groups in its structure; Fig. 1b) due to its high water solubility, biodegradability, non-toxicity [21] and because it was demonstrated to be biocompatible with pulmonary tissues ex vivo for genic therapy [22]. Considering that the polylysine can interact with anionic compounds, the combination PL–IN is postulated as a chemical entity with properties different from its precursors, as it was demonstrated for another polyelectrolyte–drug combinations [23].

Some reports related to inhalatory materials based on polyelectrolyte–drug complexes prepared by SD are available for hyaluronic acid [24], poly-epsilon-caprolactone [25], dextran [26] and alginic acid [20] combined with fluoroquinolones or atenolol. However the solid state properties of materials based on cationic polyelectrolytes and poorly water soluble drugs as well as the relationships between the process and the product quality are fields that still are required to be explored.

Therefore, the present study addressed the principles associated with the production of novel microparticles intended for pulmonary IN delivery for rheumatoid arthritis treatment. Varying the feed formulation (i.e. IN and PL/DX ratios), the powders were obtained by SD. The process performance (SD yield, air outlet temperature), product properties (IN load efficiency, moisture content, crystallinity, glass transition temperature, density, morphology and particle size distribution), the IN–PL ionic interaction (assessed by Fourier transform infrared spectroscopy, powder X-ray diffraction and thermal analysis), and IN release in vitro were extensively studied.

2. Materials and methods

2.1. Materials

Indomethacin (pharmaceutical grade, Parafarm, Saporiti, Buenos Aires, Argentina) was used as active pharmaceutical ingredient. In this work, epsilon-polylysine (food grade, Purac America, Lincolnshire, United States) was used as received from suppliers, i.e. as a mixture of polylysine:dextrin (PL:DX 50:50). Dextrin is a polysaccharide (α-1,4 poly(glucose) polymer that contains few, <5%, α-1,6 links displaying minimal branching; Fig. 1c) and, as other sugars like lactose and mannitol, allows improving flow properties [27] and storage stability [28]. This compound, which is highly water soluble, was previously used as biocompatible excipient in pulmonary product development [29]. Its association with polylysine was proposed to improve the PL conformational structure stability [28].

Lactose monohydrate (−70 + 140 ASTM Mesh, pharmaceutical grade, Parafarm, Saporiti, Buenos Aires, Argentina), potassium bromide (spectroscopic grade, Parafarm, Saporiti, Buenos Aires, Argentina), potassium phosphate monobasic (analytical grade, Anedra, Buenos Aires, Argentina), sodium hydroxide (analytical grade, Anedra, Buenos Aires, Argentina), size 3 gelatine capsules (pharmaceutical grade, Parafarm, Saporiti, Buenos Aires, Argentina) and distilled water were also used.

Please cite this article as: N.E. Ceschan, et al., Polymeric microparticles containing indomethacin for inhalatory administration, Powder Technol. (2015), http://dx.doi.org/10.1016/j.powtec.2015.02.001