Pharmaceutical Sciences
December 2017, 23, 278-284
doi: 10.15171/PS.2017.41
http://journals.tbzmed.ac.ir/PHARM

Research Article

Preparation and Characterization of Celecoxib Agglomerated Nanocrystals and Dry Powder Inhalation Formulations to Improve its Aerosolization Performance

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Article Info

Article History:
Received: 13 May 2017
Accepted: 5 August 2017
ePublished: 30 December 2017

Keywords:
-Celecoxib
-Dry powder inhaler
-Nanocrystals
-Agglomeration
-Pulmonary drug delivery

ABSTRACT

Background: Celecoxib is a non-steroidal anti-inflammatory drug used extensively in the treatment of pain, arthritis, and cancers. However, its administration is limited due to its several disadvantages including gastric irritation and hepatic first pass metabolism. Among numerous methods for pulmonary drug delivery, dry powder inhalation systems show the promising approach to be used as alternative routes for oral drug delivery. This study was conducted to develop agglomerated nanocrystals and carrier-free Celecoxib dry powder inhalation formulation for pulmonary delivery in lung cancer treatment.
Methods: Spray dried Celecoxib, Celecoxib nanocrystals, and agglomerated nanocrystals were characterized in the case of particle size distribution, crystallinity, and aerosolization efficiency including mass median aerodynamic diameter (MMAD), fine particle fraction (FPF), and geometric standard deviation (GSD) by Next Generation Impactor (NGI).
Results: Differential scanning calorimetry (DSC) and X-ray diffraction (XRD) analyses showed the lack of any interaction and polymorphism in the prepared formulations. Results showed that the optimized spray-dried formulation of Celecoxib was in the appropriate size range, and shape for pulmonary delivery. MMAD, FPF, and GSD values for spray-dried formulation were 31.93±3.93%, 4.82±0.21 µm, and 1.81±0.05, respectively.
Conclusion: Although the agglomerated nanocrystals of Celecoxib showed comparable aerosolization efficiency indexes with carrier free spray-dried Celecoxib formulation, further investigations are necessary to optimize the agglomeration process to obtain agglomerated nanocrystals of Celecoxib with improved aerosolization efficiency indexes.

Introduction

Non-small cell lung cancer (NSCLC) is currently a fatal malignant neoplasm with the highest morbidity and mortality in both sexes in comparison with other types of solid tumors. Despite the availability of new chemotherapeutic agents, the outcome for the cure of primary and metastatic lung cancer is not improved deeply and lung cancer still has the highest death rate of cancer-related mortality. Cyclooxygenase-2 (COX-2) enzyme is overexpressed in various human premalignant tissues and malignant tumors, suggesting that COX-2 is potentially associated with the pathogenesis and progress of NSCLC that causes the formation of new blood vessels within the site of malignancy.[1] Previous studies have shown that COX-2 inhibitors,

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such as Celecoxib, reduce tumor growth rate, increase cancer cells apoptosis, and show synergistic cytotoxic effects in combination with anticancer drugs they.[2] The advances in drug delivery systems for pulmonary usage have attracted noteworthy attention and great compliance of patient because of being safe drug administration route. Moreover, because of the locally and site-specific influence, drug delivery with high concentrations in the lung by avoiding the first-pass metabolism, this drug delivery route has resulted in the maximum therapeutic efficacy and minimum side effects.[3-6] The main advantages of the pulmonary route in comparison to other drug delivery systems are related to the large alveolar surface area, which is appropriate for drug absorption and wide vascularization and low proteolytic activity in the alveolar space. The capability of Celecoxib inhalation to the site of action generates more interest in its application in Celecoxib-inducing strokes and heart attacks.[7] Therefore, it is expected to obtain an optimum therapeutic outcome in patients who suffer from lung cancer since the pulmonary delivery of Celecoxib provide effective drug levels in lungs.[8,9] Recent advances in the development of novel inhalation devices make it appropriate to deliver larger drug doses to the airways and achieve a great deposition efficiency.[10] Current complications related to the common oral therapy of Celecoxib make it a good candidate for the development of pulmonary formulation as local drug delivery. Local therapy is a valued and strategic method in the management of pulmonary illnesses and targeting Celecoxib to the lung is the main strategy for improving bioavailability and reducing the systemic side effects associated with oral administration.[11] Among the three inhalation systems (e.g., pressurized metered dose inhaler,[11] dry powder inhaler (DPI),[12] and nebulizer,[13]) the DPIs are the most valuable systems in delivering particles to the respiratory tract[14] because of the propellant-free nature, high dose carrying capacity, drug stability, and high patient compliance. Dry powder formulations are generally produced by a combination of drug microparticles with a suitable solvent and larger carrier particles. Furthermore, DPIs are commonly easy to use in comparison to other types of inhalers where it is not necessary to synchronize actuation and inhalation. However, prepared powders are susceptible to cohesion and formation of larger particles that reduce the aerosolization performance. Spray drying, which has been widely employed to form dry powders, is to disperse drug solution into very small droplets by the atomizer and, subsequently, rapidly evaporate the solvent in a hot dry medium (e.g., hot air) to obtain a dry product of powder or granules. This procedure, which produces a product with a high degree of purity and narrow particle size distribution, is relatively easy to scale up for commercial production. However, there are some limitations in the application of this method especially in the case of temperature sensitive materials and high dose drugs such as Celecoxib. Spherical crystallization is a particle engineering technique where crystallization and agglomeration can be performed concomitantly in one step to transform crystals into compressed spherical form. This technique has recently attracted great attention. Thus, it seems necessary to assess and characterize these spherically agglomerated crystals by using the different parameters.[15] The formulation of carrier-free Celecoxib DPI formulation is an encouraging issue especially due to its high dose. The use of spherical agglomeration was introduced for the first time as a new method for formulation of high-dose drugs for pulmonary drug delivery system. Accordingly, in the present study, agglomerated Celecoxib nanocrystals was prepared and compared with carrier-free Celecoxib DPI formulation to improve the aerosolization efficiency of Celecoxib.

Materials and Methods

Materials

Celecoxib was kindly provided by Zahravi Pharmaceutical Company. (Iran). Ethanol 96% (v/v), acetone, isopropyl alcohol and HPLC grade acetonitrile were purchased from Merck Chemicals Company. (Germany). Hard gelatin capsule (Size No. 3) was provided from Iran Gelatin Capsule mfg Company. (Iran).

Preparation of spherical crystals and agglomerated crystals

In the preliminary studies the effects of different parameters such as drug concentration, anti-solvent/solvent ratio, temperature, stirring rate and method of drug solution addition into anti-solvent system were investigated. Acetone: ethanol mixture (1:4 mL) was found as suitable solvent due to the excellent solubility for the Celecoxib and miscibility with the distilled water, as dispersing phase (anti-solvent). Furthermore, isopropyl acetate as a bridging liquid was added to the water because of its excellent wettability for drug and immiscibility with the dispersing medium. Therefore, to prepare optimized formulation, five milliliter of drug solution (containing 300 mg of Celecoxib in the acetone: ethanol mixture) was added dropwise in to the 100 mL of distilled water under stirring rate of 1200 rpm (Silent crusher M, Heidolph, Germany) and 4 °C, using a syringe pump (SP1000, Fanavaran nano-meghyas, Tehran, Iran).

HPLC analysis

Celecoxib concentration analysis was performed by a reversed-phase HPLC system (Knauer, Germany), equipped with a UV detector. An aliquot of 20 µL

of clear sample solution was analyzed in triplicates at room temperature using a Eurospher (100-5 C18, 150 × 4.6 mm) column with a precolumn (Knauer, Germany) and mobile phase consisting of a mixture of acetonitrile: water (85:15, v/v) which eluted at a flow rate of 1.5 mL/min. Detection wavelength was set at 253 nm and calibration curve was linear in the range of 2–30 µg/mL (R^2=0.9972). There was no interference with formulation components and the samples were stable throughout the study period.

Spray drying process

The prepared solutions were spray-dried using a mini spray dryer (B-290, Büchi AG, Flawil, Switzerland) and following conditions for the spray-drying method. Inlet temperature: variable by boiling point of solvent, aspirator percent: 65%, gas flow: 60 L/min and pump degree: 10%.

Characterization of prepared formulation

The particle size and size distribution were determined by laser diffraction particle size analyzer (SALD 2101, Shimadzu, Japan). The size and size distribution were expressed by the volume median diameter (VMD) and Span value, respectively. Span value was calculated from the following equation:

$$\text{Span} = \frac{D(v90\%) - D(v10\%)}{D(v50\%)} \quad \text{Eq. (1)}$$

Where D90%, D10% and D50% are the equivalent volume diameters at 90, 10 and 50% cumulative volumes, respectively. The particles surface morphology and shape were analyzed by scanning electron microscope (SEM, MIRA3, TESCAN instrument, Czech Republic). Samples were mounted on a metal stub with double-sided adhesive tape and coated under vacuum in an argon atmosphere with gold (DST1, Nanostructured coating co., Tehran, Iran). Particle size was evaluated by measuring the Ferret diameters of at least 300 particles shown in SEM using image analysis software (Image-Pro Plus 6; Media Cybernetics, Silver Spring, USA).[16] A differential scanning calorimeter (DSC-60, Shimadzu, Japan), calibrated by indium, was employed to assess enthalpy and melting points of the formulations. Samples (5 mg) were heated in the range of 25–210 °C at a scanning rate of 10 °C/min in aluminum pans under nitrogen gas. The melting points and enthalpies of fusion were calculated using the TA-60WS software.[17] XRD analysis was performed using an X-ray diffractometer (D-5000, Siemen, Germany, 2° to 70°) to evaluate the crystalline structures. Diffractograms were run at scanning speed of 2º/min. The diffraction pattern was measured using a Cu-Kα radiation source (30 mA and 40 kV).

Aerosolization efficiency study

The aerosolization efficiency of Celecoxib powder, nanocrystals, agglomerated nanocrystals and spray-dried formulations were analyzed according to the USP monograph using the Next Generation Impactor (NGI) (Copley Scientific, Nottingham, UK. The powders (10 mg) were filled into gelatin capsules (size 3) and aerosolized using an Aerolizer® (Novartis, Switzerland), a commercially accessible, breath-actuated, single dose capsule-based DPI. To prevent inter-stage losses and ensure efficient particle capture, due to particle bounce, the particle collection surface of each stage was coated with Tween® 80 by immersing into Tween® 80 ethanolic solution (1%) and complete drying under the fume hood. DPI was attached to the induction port of the NGI using a molded silicone adapter and impelled over 4 seconds at a flow rate (DFM 2000, Copley Scientific, Nottingham, UK) of 60 L/min. After aerosolization all collection surfaces were washed with ethanol to dissolve Celecoxib. Capsules were also gathered after actuation for the study of remained powder and drug content in each phase was determined (linear in the range of 2-30 µg/mL, r^2=0.9998. Fine particle fraction (FPF) depicts the percentage of emitted particles with MMAD of 5 µm or less.[18] The Mass median aerodynamic diameter (MMAD) is defined as the diameter at which 50% of the particles (by mass) are larger and 50% are smaller, whereas the FPF relates to the fraction of drug carried in particles with a diameter of <5µm. FPF evaluates the fraction of particles assumed to deposit deep within the lung). MMAD and geometric standard deviation (GSD) were calculated with Copley Inhaler Testing Data Analysis Software (CITDAS V3.10) based on the dose collected on stages 1 through 7 and the micro-orifice collector (MOC), as expressed in the USP 32-NF 27 General Chapter 601: Aerosols, Nasal sprays, Metered-dose inhalers, and Dry powder inhalers.[19]

Statistical analysis

Data are expressed as a mean value ± standard deviation (SD). Statistical analysis was performed using a one-way analysis of variance (ANOVA) test using SPSS software (version 16.0, Chicago, IL, USA). A P value <0.05 was considered statistically significant.

Results

Characterization of nanocrystals and agglomerated nanocrystals

After preliminary studies and preparation of different formulations with different conditions, particle size analysis demonstrated that, decreasing the drug concentration, increasing solvent/non-solvent ratio, increasing stirring rate up to 1200 rpm, decreasing the non-solvent temperature from 25 to 4°C, and dropwise addition of solvent into non-solvent result in particle size decrease.

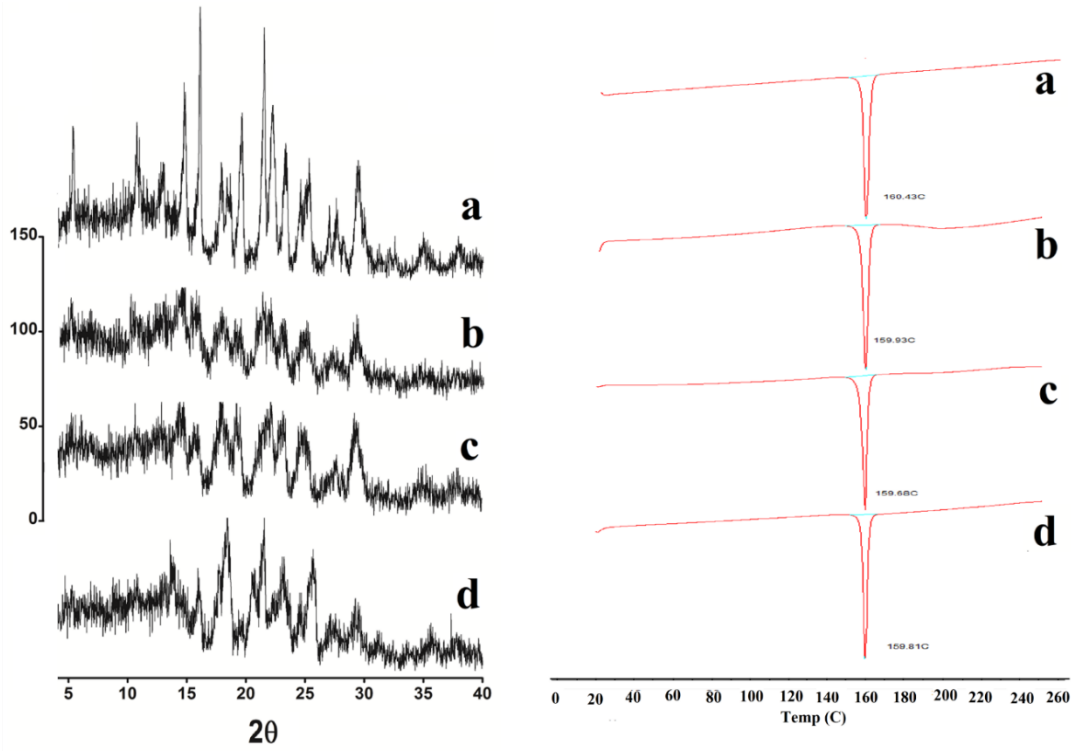

Figure 1. The X-Ray diffraction patterns (right) and DSC thermograms (left) of a) pure Celecoxib, b) Celecoxib nanocrystals, mc) agglomerated Celecoxib nanocrystals and d) spray-dried formulation.

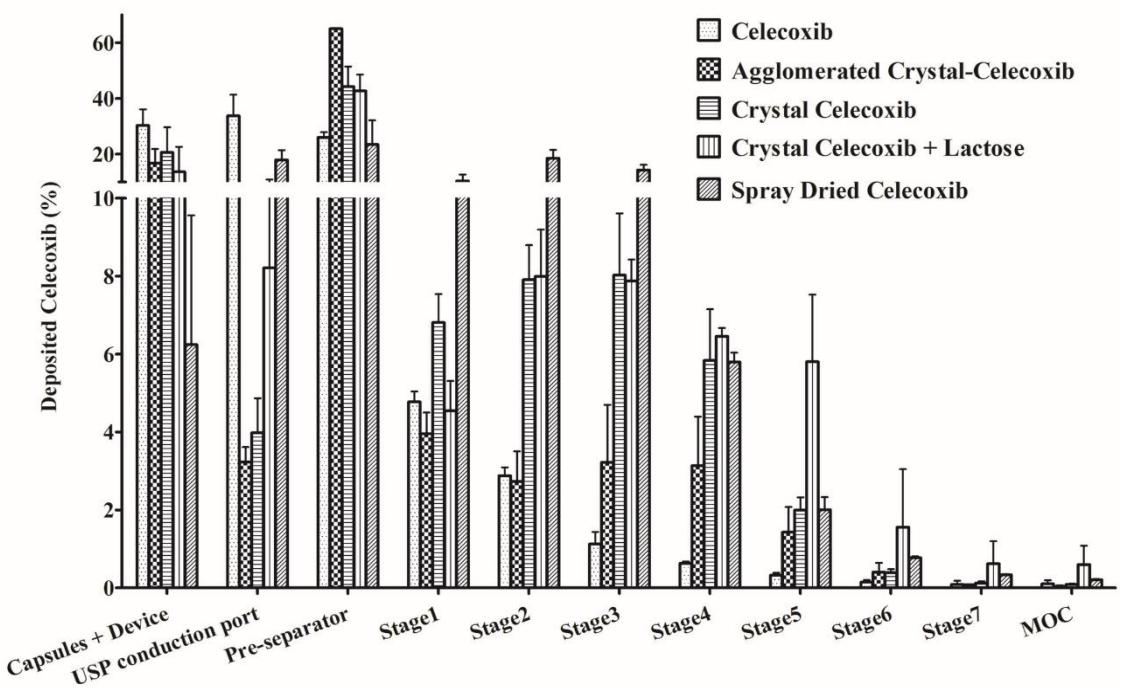

Figure 2. Comparison of the Celecoxib amount of injected pure Celecoxib, Celecoxib Crystal, agglomerated Celecoxib crystal and spray-dried Celecoxib deposited in various stages of NGI (data presented as mean ± SD, n= 3).

Furthermore, primary studies also showed that although acetone is a suitable solvent for Celecoxib, the solubility of the Celecoxib in bridging liquid inhibited the preparation of nanocrystals.

Therefore, the mixture of acetone-ethanol was used to increase the solubility of Celecoxib, which increases the solubility up to six times. The number (NMD) and volume (VMD) mean diameters of nanoparticles prepared via liquid anti-solvent precipitation technique were 93 and 113 nm, respectively. The small difference between VMD and NMD indicates the homogeneity and ideal narrow size distribution of the prepared nanoparticles.[17] The optimized formulation was

used for the preparation of DPI by co-spray drying with different ratios of mannitol as discussed in the next section.

XRD and DSC analysis

XRD and DSC analyses were performed in order to assess possible relevant modifications of crystallinity. Figure 1 shows that the XRD pattern and DSC thermograms of pure Celecoxib, Celecoxib nanocrystals, agglomerated Celecoxib nanocrystals, and spray dried-formulation. Both experiments indicated that Celecoxib exists in an amorphous state in the nanocrystals, agglomerated nanocrystals, and spray-drying powder. Lack of any sharp peak in the XRD pattern of pure mannitol indicates its conversion into the amorphous form after spray drying due to the probably rapid conversion of a mannitol solution into the solid state as a result of the absence of enough time for the ordering of molecules. The appearance of weaker peaks associated to Celecoxib in spray-dried powders demonstrates the decreasing in the initial crystalline state of Celecoxib, which resulted in better inhalation performance. Therefore, it can be concluded that spray drying could not influence its semi-crystalline structure.

Evaluation of inhalation performance with NGI

Inhalation performance of pure Celecoxib, Celecoxib Crystal, agglomerated Celecoxib crystal, and spray-dried powder of Celecoxib crystal with and without lactose was compared using a Next Generation Impactor (NGI) apparatus (Table 1).

These results show that pure Celecoxib had the worst and spray-dried formulation showed the best inhalation performance in the analysis by NGI. Agglomeration did not improve significantly the aerosolization performance of Celecoxib probably due to their hardness, which results in a difficulty in breaking the crystals and exiting from the aerosolizer. Furthermore, there was no significant difference between Celecoxib crystals and Celecoxib crystals spray-dried by lactose as a carrier ($P = 0.234$).

Discussion

Celecoxib is a poorly water-soluble drug classified as biopharmaceutical classification system class II drug (high permeability and low solubility) and poor oral bioavailability (22–40 %).[20] High oral or intravenous dose should be administered to obtain a therapeutic drug level at the site of lung carcinoma, which improves the incidence of undesirable side effects. Hence, pulmonary drug delivery application is considered as an alternative and potential delivery route to the cure of lung cancer. Local delivery of Celecoxib to the lungs via nanoparticles is a novel therapeutic option for the use of Celecoxib in lung cancer. In this regard, the in vivo assessment of Celecoxib aerosol brings more attention to this issue considering the recent reports on Celecoxib-inducing strokes and heart attacks in the Phase III cancer investigation after oral administration of Celecoxib.[7] Pulmonary delivery is considered as a rapid clinical response and the capability to bypass therapeutic barriers including poor gastrointestinal absorption and first-pass hepatic metabolism since it reduces dose and side effects.[21] For the formulation of suitable DPI, developed particles should have a mean aerodynamic size below than 5 µm.[22] This requirement is fulfilled when drug was co-spray-dried with mannitol. After nanoparticles preparation, the next phase is the control of aggregation for the preparation of respirable particles (1-5 µm). In this connection, spray drying technique has been introduced as a suitable method for preparation of particles in this range. Spray drying is a one-step and low-cost pharmaceutical process extensively used in the preparation of dry powder formulations since it offers a number of potential benefits over lyophilization method and development of uniformly sized particles with preferred aerosolization properties.[23] Spherical agglomeration method is a specified and modern method successfully employed to increase solubility, flowability, compressibility, wettability, packability, and bioavailability of numerous poorly water soluble drugs. Several methods such as solvent crystallization method, solvent agglomeration technique quasi-emulsion diffusion method, ammonia diffusion technique, and neutralization method have been studied in previous works. The present study paved the way to further investigate the optimization of these methods to obtain agglomerated Celecoxib nanocrystals with desired characteristics and aerosolization efficiency indexes.

Table 1. Aerosolization efficiency indexes of injected pure Celecoxib, Celecoxib Crystal, agglomerated Celecoxib crystal and spray-dried powder (data presented as mean ± SD, n= 3).

Formulation	[a]FPD (µg)	[b]FPF (%)	[c]MMAD (µm)	[d]GSD
Celecoxib powder	0.59 ± 0.05	4.18 ± 0.33	7.68 ± 0.29	2.39 ± 0.14
Celecoxib Crystal	3.38 ± 0.49	22.87 ± 3.92	4.29 ± 0.29	1.98 ± 0.05
Celecoxib Agglomerate	1.30 ± 0.34	10.54 ± 3.87	4.10 ± 0.49	2.22 ± 0.14
Spray dried	4.80 ± 0.26	31.93 ± 3.93	4.82 ± 0.21	1.81 ± 0.05
Celecoxib Crystal+ lactose	1.30 ± 0.34	28.98 ± 5.46	3.30 ± 0.99	2.30 ± 0.41

[a]Fine particle dose (FPD) [b]Fine particle fraction (FPF) [c]Mass median aerodynamic diameter (MMAD) [d]Geometric standard deviation (GSD)

Conclusion

Liquid anti-solvent-diffusion method was successfully used to prepare Celecoxib nanocrystals. For this purpose, Celecoxib powder was spray-dried with and without lactose to produce microparticles with suitable size for DPIs formulation. Results indicated that although agglomeration technique could significantly improve the aerosolization efficiency of Celecoxib nanocrystals, the aerosolization efficiency indexes are comparable with spray-dried Celecoxib powder. These finding suggested that further investigations are necessary to optimize the agglomeration process conditions, such as kind of bridging liquids, the temperature of agglomeration process, and stirring rate and to obtain the powder with high aerosolization efficiency indexes. Due to the simplicity of this method and its lack of need for using a carrier, especially for high dose drug as well as temperature sensitive drugs, this method draws promising horizons for the preparation of powder for pulmonary drug delivery systems.

Acknowledgment

This paper was extracted from Pharm.D thesis No. 3814 that was submitted to the Faculty of Pharmacy of Tabriz University of Medical Sciences and financially supported by grant (No. 91/82) from the Drug Applied Research Center of the same university.

Conflict of interests

The authors claim that there is no conflict of interest.

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