

Development of Carrier Free Montelukast Dry Powder Inhalation Formulation

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■ ABSTRACT

While there are several approaches for treating pulmonary diseases, dry powder inhaler systems for pulmonary delivery have the encouraging potential to be alternative routes to oral drug administration. Particle engineering for pulmonary delivery can be performed by changing spray-drying conditions and formulation parameters which have an effect on the characteristics and morphology of particles. The present study aimed to prepare Montelukast sodium microparticles using the spray-drying technique to improve their respirable fraction and, as a result, their systemic bioavailability. In this study, microparticles were prepared using optimized process parameters and were characterized for aerosolization efficiency and different physicochemical parameters, including morphology, fine particle fraction (FPF), mass median aerodynamic diameter (MMAD), and geometric standard deviation (GSD) using scanning electron microscope (SEM), powder X-ray diffractometer, and Next Generation Impactor. Moreover, ammonium bicarbonate was used to reduce the aerodynamic diameter and aggregation of microparticles. SEM images showed that microparticles were in the appropriate range and had the appropriate shape and surface characteristics for pulmonary delivery. FPF, MMAD, and GSD for the optimized formulation were $48.3 \pm 5\%$, $3.63 \pm 5.4 \mu\text{m}$, and 1.86 ± 0.05 , respectively. The addition of ammonium bicarbonate did not improve the aerosolization efficiency indexes. An

■ KEY WORDS

- Montelukast sodium
- Dry powder inhaler
- Spray drying technique
- Pulmonary drug delivery
- DPI

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evaluation of the aerosolization performance of spray-dried formulations indicated that the concentration of feed solution and solvent type substantially influenced aerosolization efficiency.

■ ZUSAMMENFASSUNG

Zwar gibt es verschiedene Ansätze für die Behandlung von Lungenerkrankungen, Trockenpulverinhalatorsysteme zur pulmonalen Verabreichung haben jedoch vielversprechendes Potenzial als alternative Darreichungsform zur oralen Verabreichung des Arzneimittels. Partikeltechnik zur pulmonalen Verabreichung kann durch Änderung der Sprühtrocknungsbedingungen und Formulierungsparameter, die Einfluss auf die Eigenschaften und Morphologie der Teilchen haben, durchgeführt werden. In der vorliegenden Studie wurden Montelukast-Natrium-Mikropartikel unter Verwendung der Sprühtrocknungstechnik zubereitet, um ihren lungengängigen Anteil und, infolgedessen, ihre systemische Bioverfügbarkeit zu verbessern. In dieser Studie wurden die Mikropartikel mit optimierten Prozessparametern hergestellt und wurden mit Rasterelektronenmikroskop, Pulver-Röntgen-Diffraktometer und Next-Generation-Impactor für die Aerosolisierungseffizienz und die unterschiedlichen physikochemischen Parameter, einschließlich Morphologie, Feinpartikelfraktion (FPF), medianem aerodynamischem Massendurchmesser (MMAD) und geometrischer Standardabweichung (GSA), charakterisiert. Außerdem wurde Ammoniumbicarbonat verwendet, um den aerodynamischen Durchmesser und die Aggregation der Mikropartikel zu verringern. Rasterelektronenmikroskopbilder zeigten, dass Mikropartikel in dem geeigneten Bereich lagen und die geeignete Form und Oberflächenbeschaffenheit für die pulmonale Verabreichung hatten. FPF-, MMAD- und GSD-Werte zur opti-

mierten Formulierung lagen bei $48.3 \pm 5\%$, 3.63 ± 5.4 bzw. 1.86 ± 0.05 . Die Zugabe von Ammoniumbicarbonat verbesserte die Aerosolisierungseffizienzindizes nicht. Eine Bewertung der Aerosolisierungsleistung sprühgetrockneter Formulierungen zeigt, dass die Konzentration der Beschickungslösung und des Lösungsmitteltyps die Aerosolisierungseffizienz wesentlich beeinflusst.

1. Introduction

Asthma is a hypersensitivity disorder of the airways, characterized by chronic inflamed and easily collapsible airways as well as reversible airway obstruction [1]. Numerous approaches can serve as treatments for this disease, particularly the pulmonary drug delivery route, which represents an appealing and encouraging way to localize treatment of respiratory diseases like asthma [2]. The main advantages of the pulmonary route compared with other drug administration routes are associated with the large alveolar surface area suitable for drug absorption and extensive vascularization with the relatively low proteolytic activity in the alveolar space [3]. Montelukast is the most specific and powerful leukotriene receptor antagonists used as a controller medication in allergic and viral-induced asthma [4]. It is also used to prevent and treat asthma [5], bronchial hyper reactivity [6], bronchial obstruction [7] and chronic asthma attacks [8]. The main drawback of the conventional Montelukast oral therapy is associated with hepatic first pass metabolism resulting in a short biological half-life and reduction in drug bioavailability. Harugeri et al. reported that patients suffering from chronic asthma and treated with Montelukast showed signs of jaundice and hepatomegaly [9]. Current problems associated with the conventional oral therapy of Montelukast make it a perfect candidate for the development of a pulmonary formulation for localized drug delivery. Targeting Montelukast to the lung is a primary strategy for improving bioavailability and reducing the systemic side effects and hepatotoxicity associated with oral administration [10]. Among the three inhalation systems, pressurized metered-dose inhaler [10], dry powder inhaler (DPI) [11], and nebulizer [12], the DPI is most advantageous in delivering microparticles to the respiratory tract by virtue of its propellant-free nature, high patient compliance, high dose-carrying capacity, and drug stability. Rapid developments have been made in recent years to realize the full potential of lungs for local and systemic treatment of diseases, and thus have made DPIs the second most frequently used inhalation device for pulmonary drug administration [13]. Dry powder formulations are usually prepared by mixing drug microparticles with suitable solvent and larger carrier particles. Drug deposition in the lungs is mainly controlled by its aerodynamic diameter [14] in which particles larger than $5\ \mu\text{m}$ will mostly be trapped by oropharyngeal deposition and incapable of reaching the lungs, while particles smaller than $1\ \mu\text{m}$ are mostly exhaled without deposi-

tion [15]. Previous studies have demonstrated that the physical properties of particles including size and morphology can be influenced by the addition of ammonium bicarbonate (ABC). During spray drying, ABC readily transforms into the gaseous components, carbon dioxide and ammonia, resulting in the formation of porous particles [16]. Therefore, adding of ABC to formulations intended for inhalation reduces their density by forming porous particles which may improve the powder aerodynamic characteristics. The aim of the current study was to develop and characterize an inhaled formulation of Montelukast and novel spray dried microparticles in order to improve the respirable fraction of the formulation to the lungs. To this end, different ratios of water and ethanol mixture were used to prepare microparticles in order to produce efficient and optimized microparticles with a better morphology, fine particle fraction and mass median aerodynamic diameter. ABC was also used to reduce the aerodynamic diameter of the microparticles and to decrease their aggregation capacity.

2. Materials and methods

2.1. Materials

Montelukast powder was obtained from Triveni Chemicals Company (India). Ethanol was purchased from Golriz Company (Iran). Tween® 80, phosphoric acid and acetonitrile were supplied from Merck Company (Germany). Ammonium bicarbonate was obtained from Sigma Aldrich Company (Germany). All other chemicals and reagents were of analytical grade and used as received.

2.2. Preparation of Montelukast microparticles using spray drying technique

Formulations of Montelukast were prepared employing spray drying technique. Different formulations of microparticles were prepared and formulation parameters as well as process variables were optimized (Tab. 1). Briefly, optimized formulation containing 1.25 g Montelukast powder was dissolved in a mixture of distilled water and ethanol (1:2) at $50\ ^\circ\text{C}$ under continuous stirring (1 400 rpm) for 150 minutes. Subsequently, obtained solution was spray dried by using a mini spray dryer (B-290-Advanced, BUCHI, Switzerland) under the optimum conditions (Nozzle: 0.7 mm, pump pressure: 10 Pascal, aspirator: 70 %, input temperature: 90 and flow rate: 6 L/h) and obtained powder was collected from the spray dryer cyclone immediately after spray drying in order to avoid absorption of moisture. During spray drying method the surface structure of the microparticles might be altered due to the production of inert gaseous components by immediate transformation of ammonium bicarbonate. Therefore, to investigate its effect on the surface of microparticles, ammonium bicarbonate was added to the formulation.

2.3. Determination of Montelukast deposition parameters using NGI

The aerodynamic diameter, aerosolization efficiency and deposition characteristics of the dry powders were assessed using a dry-powder inhalers Aerolizer® (Novartis, Switzerland) connected to NGI with Pre-Separator and United States Pharmacopeia (USP) Induction Port. The induction port was used to connect the device to the inhaler and con-

■ **Table 1**

Different formulations of Montelukast microparticles.

Formulation code	Ethanol (mL)	Water (mL)	ABC (%)	Yield (%)	FPF (%)	MMAD (μm)	GSD
1	20	10	-	68	48.3 \pm 5.4	3.5 \pm 0.1	1.9 \pm 0.1
2	20	10	1	72	46.1 \pm 6.2	3.6 \pm 0.4	1.8 \pm 0.1
3	20	10	3	64	41.1 \pm 8.3	3.3 \pm 0.5	1.9 \pm 0.1
4	20	10	6	57	43.5 \pm 9.9	3.9 \pm 0.6	1.7 \pm 0.2
5	20	10	30	46	35.5 \pm 7.3	4.8 \pm 0.2	1.6 \pm 0.1
6	30	-	-	63	37.9 \pm 3.7	3.3 \pm 0.6	1.8 \pm 0.1
7	3	-	-	24	18.4 \pm 2.5	4.3 \pm 0.2	1.9 \pm 0.2

^aAmmonium bicarbonate

^bFine Particle Fraction

^cMass Median Aerodynamic Diameter

^dGeometric Standard Deviation

nected to impactor via pre-separator to avoid overloading at the first stage. Hard gelatin capsules (size No = 3) were filled with 10 mg of spray dried powder. The particle collection surface of each stage was coated with Tween 80 to ensure efficient particle capture and prevent inter-stage losses due to particle bounce. To this end, all eight collection cups of the NGI were soaked into ethanol solution containing 1 % Tween 80 and subsequently the coated cups were placed under the fume hood to evaporate ethanol completely. Subsequently, the cups were placed into the apertures in the cup tray and the impactor lid was closed with the sealed body attached. The flow rate was achieved using a critical flow controller and fixed at 60 L/min. One capsule was placed in the Aerolizer and punctured according to the device use instructions. After running the vacuum pump, the pump was operated for 4 seconds in which a steady flow rate of 60 L/min was achieved and the dose was released. Capsules were gathered after actuation to measure the remaining powder. A mixture of ethanol and water was used as a washing solvent for Montelukast. The capsule shells, Pre-Separator, USP induction port and NGI stages were washed with a suitable amount of ethanol and water using micropipettes. Mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were calculated with CITDAS V3.10, a data processing software (Copley Scientific, Nottingham, UK) based on the dose deposited on stages 1 to 7 and the micro-orifice collector (MOC), as defined in the USP. Fine particle fraction (FPF) was determined from the amount of Montelukast collected from stages 2 to MOC, which represents the percentage of emitted particles with an MMAD of 4.5 μm or less. FPF values estimates the fraction of particles expected to deposit deeper in the lungs.

2.4. Quantitative HPLC analysis of Montelukast

Quantitative analysis of Montelukast was performed using an HPLC system (Knauer, Germany) employing a C18 column (250 \times 4.6 mm, 5 μm) equipped with a precolumn. A mixture of acetonitrile, distilled water and Ethanol (90:5:5), with a flow rate of 2 mL/min, was used as mobile phase and degassed by a bath sonicator for 10 minutes. Detection has been performed in a wavelength of 225 nm. The calculation of noise to peak ratio concluded that LOD and LOQ were 15 and 45 ng/ml, respectively.

2.5. Scanning Electron Microscopy (SEM)

The SEM photographs of prepared microparticles by spray drying method were obtained using scanning electron microscope (MIRA3

TESCAN, UK) operating at 15 kV. The specimens were mounted on a metal stub with double-sided adhesive tape and coated under vacuum with gold in an argon atmosphere prior to observation using a direct current sputter technique (EMITECHK450X, England).

2.6. Powder X-Ray Diffraction (XRD) study

X-ray diffractograms were obtained using an X-ray diffractometer (Siemens D500, Munich Germany) and Cu-K α radiation ($\lambda=1.5406$). Diffractograms were run at scanning speed of 2 $^\circ$ /min and a chart speed of 0.6 $^\circ$ /min.

2.7. Differential scanning calorimetry (DSC)

Thermograms of unprocessed and spray dried Montelukast were recorded on a DSC (Perkin Elmer, Santa Carla, United States). Each sample (6 mg) was scanned in an aluminum pan at a heating rate of 20 $^\circ\text{C}/\text{min}$ over the range of room temperature-250 $^\circ\text{C}$. An empty aluminum pan was used as reference.

2.8. Statistical analysis

Data are expressed as a mean value \pm standard deviation (SD). Statistical analysis was performed using a one-way analysis of variance (ANOVA) with multiple comparisons between deposition data by a Tukey honest significant difference (HSD) test using SPSS software (version 13.0, Chicago, IL, USA). A P value <0.05 was considered statistically significant.

3. Results

3.1. Determination of Montelukast deposition parameters using NGI

The effects of different formulation parameters on production yield and deposition parameters are shown in Table 1. As can be seen, by increasing the amount of ABC the production yield was reduced. Although ABC was not used in formulations 1 and 6, they showed acceptable yield values. Results also showed that increasing the ABC concentration, resulted in no considerable change in FPF and MMAD values. Furthermore, in formulations 6 and 7, 1.25 g of Montelukast was dissolved in

30 and 3 mL of ethanol, respectively. The obtained results showed that by increasing Montelukast concentration 10-fold, production yield, MMAD and FPF values were reduced.

3.2. SEM analysis

To evaluate the microparticles morphology, diameter and distribution, the obtained powders were analyzed by SEM. Figure 1 illustrates the morphology of different formulations with different amounts of ABC and compares particle shape, order and distribution. As can be seen in fig. 1b to 1f, increasing the concentration of ABC, reduced the smoothness and regularity of the particles. Furthermore, by increasing the concentration of Montelukast, the quality, regularity and scattering of particles were considerably reduced (fig. 1b and 1j). Accordingly, storing the particles in desiccators for one month, preserved the powder from moisture absorption and reduced particle quality (fig. 1b and 1h).

3.3. XRD and DSC analysis

XRD and DSC analysis were performed on the carrier particles in order to assess possible relevant modifications of crystallinity. Figure 2 shows the X-ray diffraction pattern and DSC thermograms of Montelukast powder before and after spray drying. DSC thermograms of Montelukast is well-matched with previously reported articles [17, 18]. Both experiments indicated that Montelukast was presented in the amorphous structure by spray drying procedure.

4. Discussion

A drug is a combination of pharmacological effects as well as pharmaceutical properties. Pulmonary drug delivery is one of the most important approaches for drug delivery systems. Spray drying is one of the best ways to obtain a dry powder inhaler with the desired quality [19, 20]. Although spray drying is a great approach to producing dry powders for inhalation, the design parameters of the process for preparing optimized powder with desired conditions is still a serious challenge [21]. Several dry powder formulations such as drug-sugar combinations [22], drug-lipid combinations [23], and liposomal [24] dry powder were studied to determine the behavior, morphology, stability and release characteristics of aerosols. Investigators in this research studied the preparation of a dry powder inhaler of Montelukast without using a carrier. Changing the properties of the spray solution and the process conditions produced micronized particles with suitable aerodynamic properties for pulmonary drug delivery. Initially, Montelukast included big dispersed particles, however, the spray drying process changed the particles to micronized spherical shape ones. Their shape is one main characteristic affecting

pulmonary drug delivery. Although the particles used for pulmonary drug delivery have different forms, the critical factor in selecting them is their aerodynamic diameter. Using water and ethanol produced particles with a smooth surface and without aggregated particles, while the aggregation of particles in the formulation with ethanol was clearly observed. The particle aggregation rate is inversely related to drug deposition in the lungs results of FPF and MMAD verified this fact. The maximum FPF value (46 %) was observed in formulation F1 indicating it had suitable pulmonary properties and formulation F7 with the lowest FPF (18.45 %) was not suitable for pulmonary drug delivery. On the other hand, formulation F1 with a MMAD value of 3.6 μm was relatively suitable for pulmonary drug delivery compared to formulation F5 with a MMAD = 8.4 μm . It should be further noted that formulation F1 also had favorable properties in terms of morphology, and the production yield value for the spray drying process was 68 %, which is acceptable. Therefore, using ethanol and water as a solvent produced a powder inhaler with favorable characteristics. In addition to micronizing by spray drying, providing low-density particles (e.g., hollow or porous particles) to improve the efficiency of drug inhalation is desirable. Particle surface characteristics such as roughness and surface energy are also important for improving particle dispersion [25]. Therefore, further studies were performed to investigate the morphology of the particles such as with the addition of ABC. During spray drying, the ABC was readily transformed to the gaseous components, carbon dioxide and ammonia, which resulted in the formation of porous particles. In previous research, the addition of ABC increased yield and improved the quality of the obtained powder [16]. Conversely, the outcomes of this study indicated the efficiency of spray drying was reduced when the amount of ABC was increased. Formulation F1 without ABC in its formulation showed the desirable efficiency which represents the negligible impact of ABC on yield and quality of the produced powder. This may be due to the nature and physicochemical properties of Montelukast. Based on SEM micrographs, it can be concluded that the quality and particle dispersion of formulations containing both ethanol and water are better than those of formulations containing ethanol. Furthermore, increasing the concentration of Montelukast not only resulted in a reduction in production yield values, but also in poor and undesirable powder quality in formulation F7. Both DSC and XRD experiments indicated that Montelukast was in amorphous state and as predicted, its structure did not change through spray drying procedure. Usually, spray drying process leads to changes in the crystalline structure of drug to amorphous one. In this case, the drug turns to the crystalline structure during the storage time of the product which consequently causes non-predictable drug performance. Montelukast sodium is a hygroscopic material and its

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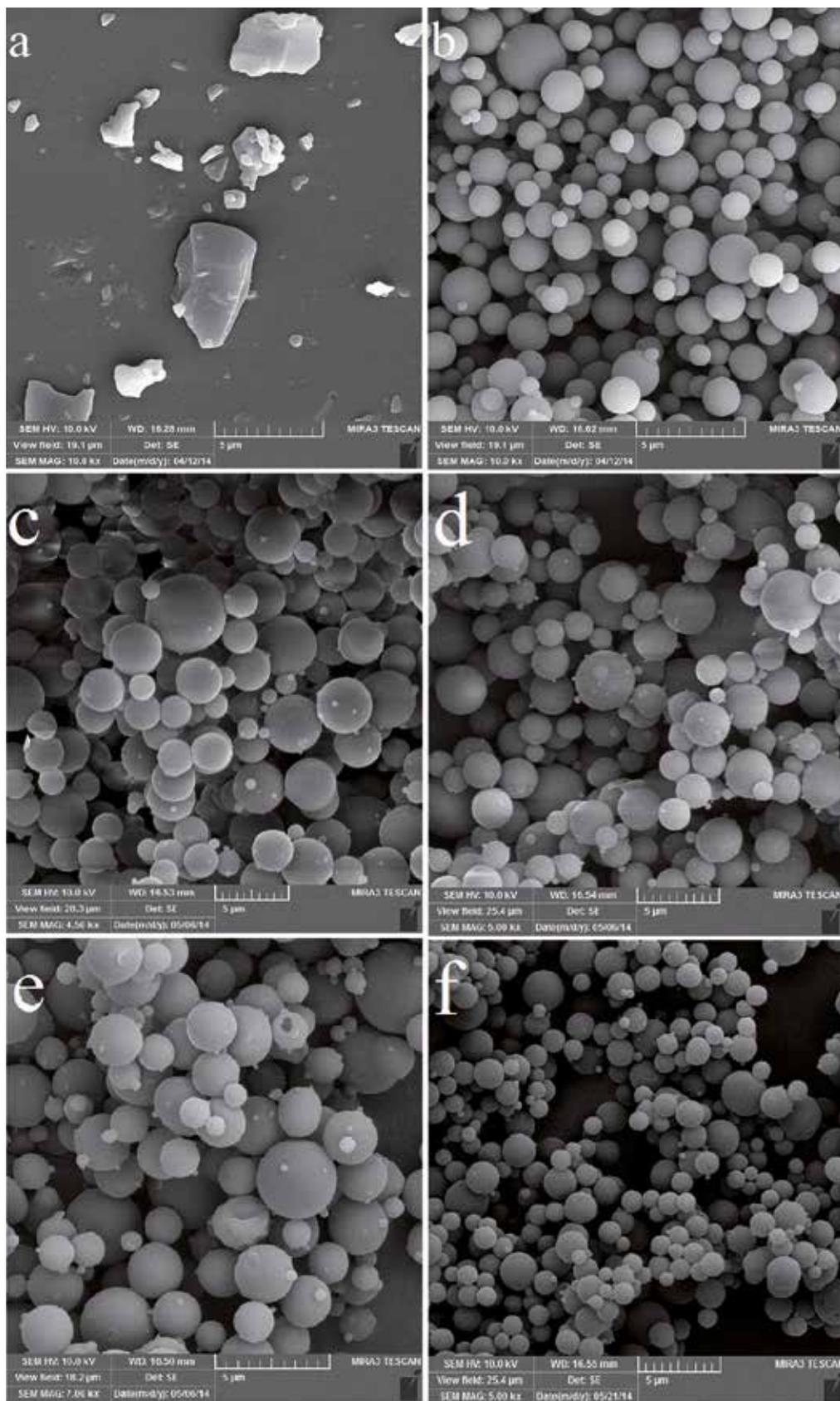


Fig. 1: Scanning electron microscopy images of (a) unprocessed Montelukast, (b) F1, (c) F2, (d) F3, (e) F4, (f) F5, (g) F1 after one month of storage in a desiccator, (h) F6 (low magnification), (i) F6 (high magnification), and (j) F7 (source: all figures made by the authors).

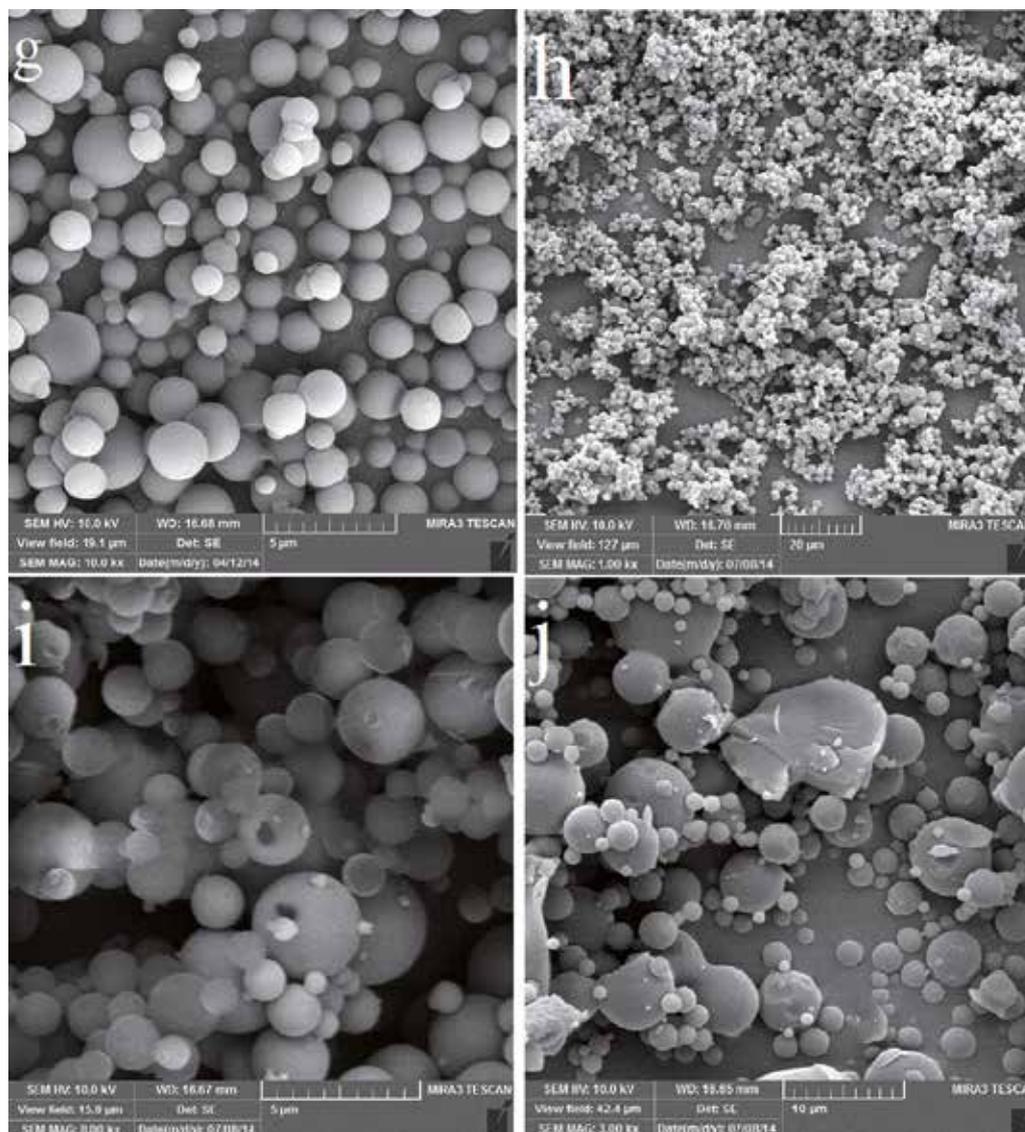


Fig. 1: continued

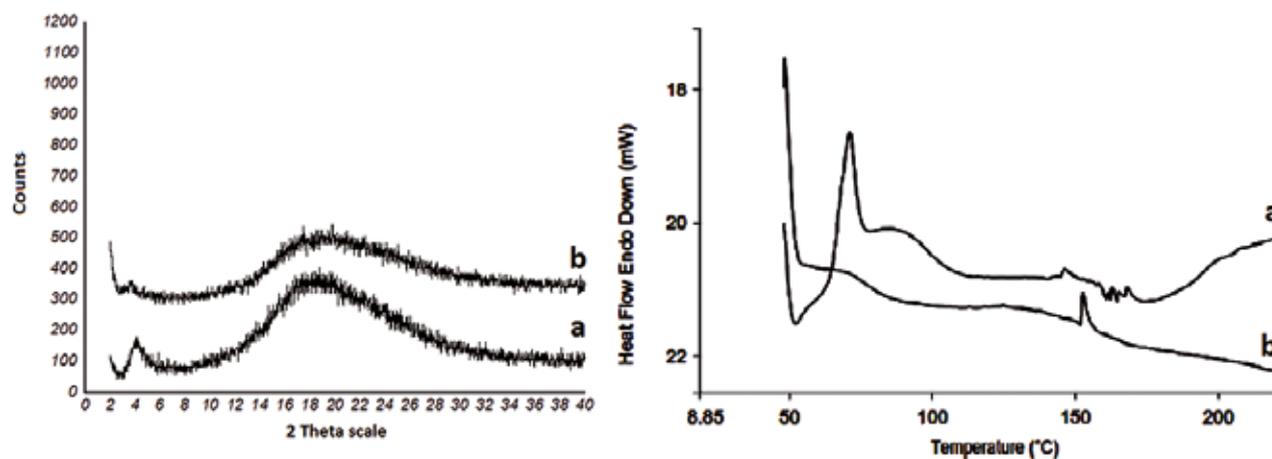


Fig. 2: X-ray diffraction pattern (left) and differential scanning calorimetry thermograms (right) of Montelukast powder (a) unprocessed, and (b) after spray drying.

hygroscopicity will certainly increase following spray drying due to an increase in its amorphous status. To avoid the water uptake by spray-dried powder, it was collected instantly after spray drying, poured in a tightly closed container and kept at a desiccator until further experiments. The lack of broad endothermic peak around 100 °C in DSC thermograms of processed Montelukast indicated that the tested (hygroscopic) material did not adsorb higher amounts of water during and after the spray drying procedure. This proper packaging of spray-dried Montelukast powder to avoid water adsorption should be considered by the pharmaceutical industries, as well.

5. Conclusion

The use of aerosol therapy for drug delivery to lungs in asthma and chronic obstructive pulmonary diseases has increased considerably in recent years, and compared to other dosage forms, interest in DPIs has increased in recent decades. Currently, the performance of DPI inhalers is being improved by changing formulation strategy as well as drug and carrier particle engineering. The main objective with inhalers is to obtain powders with high pulmonary deposition which can be highly affected by the physicochemical characteristics of drugs. This can be achieved with the suitable solution and optimization of spray drying conditions. Changes in the concentration of feed solution, the added amount of ammonium bicarbonate in different levels, and solvent type in the formulation of Montelukast powder by spray drying procedure resulted in formulations with optimized aerosolization yield, fine particle fraction and mass median aerodynamic diameter. Data from the present study indicates that the simple, one-step, low-cost, and rapid-acting characteristics of spray-drying make it a promising method for producing the DPI formulation of Montelukast on an industrial scale.

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Conflict of interest

The authors report no conflicts of interest.

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