Journal of Aerosol Science 175 (2024) 106290

Contents lists available at ScienceDirect

Journal of Aerosol Science

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

Preparing dry powder inhalation formulation of salbutamol sulfate using an ultrasonic atomizer device

Shadi Yaqoubi [a,1], Mohaddese Sokuti [b,1], Sahand Mazloum-Ravasan [c], Kofi Asare-Addo [d], Hamed Hamishehkar [e,**], Ali Nokhodchi [f,g,*]

[a] Biotechnology Research Center and Research Center for Integrated Medicine in Aging, Tabriz University of Medical Sciences, Tabriz, Iran
[b] Students Research Committee, and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran
[c] Research Center for Pharmaceutical Nanotechnology, Tabriz University of Medical Sciences, Tabriz, Iran
[d] Department of Pharmacy, University of Huddersfield, Huddersfield, HD1 3DH, UK
[e] Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[f] Lupin Inhalation Research Center, 4006 NW 124th Ave., Coral Springs, FL, 33065, USA
[g] School of Life Sciences, University of Sussex, Brighton, BN1 9QG, UK

ARTICLE INFO

Keywords:
Salbutamol sulfate
Particle engineering
Ultrasonic nebulization
Ultrasonic spray pyrolysis
Dry powder inhaler

ABSTRACT

Inhaled particles must possess certain morphological characteristics to ensure effective drug delivery to the targeted site in the lungs. A modified version of ultrasonic spray pyrolysis was employed to prepare salbutamol sulfate in the form of dry powder. A solution of salbutamol sulfate was atomized using ultrasonic nebulization, and the droplets were transformed into solid drug particles through exposure to high temperature airflow. The engineered salbutamol sulfate samples underwent physical characterization, including particle size, morphology, thermal behavior, and crystallinity analysis. The aerodynamic particle size distribution (APSD) and in vitro deposition of the dry powder inhalation formulation were assessed using the Next Generation Impactor (NGI). The salbutamol sulfate dry powder prepared by the ultrasonic atomizer exhibited an aerodynamic diameter ranging from 1 to 5 μm, as supported by the SEM images. X-ray diffraction (XRD) and differential scanning calorimetry (DSC) results showed a significant drop in the crystallinity of the engineered particles. Aerosolization performance studies demonstrated a fine particle fraction (FPF) value (below 5 μm) of 25% for the engineered salbutamol sulfate produced using the ultrasonic atomizer technique, which is acceptable for inhalation purposes. Based on the observed results, this newly introduced method appears to be suitable for producing dry powder formulations of different drugs, with a minimized need for the use of surfactants or stabilizers in the formulation.

1. Introduction

Pulmonary drug delivery is a highly favored route for advanced drug delivery (Zhong et al., 2018), primarily aiming at localized drug delivery to the lungs for targeted treatment of lung diseases (ElKasabgy et al., 2020; Son & McConville, 2008). To achieve

* Corresponding author. Lupin Inhalation Research Center, 4006 NW 124th Ave., Coral Springs, FL, 33065, USA.
** Corresponding author.
E-mail addresses: Hamishehkar.hamed@gmail.com (H. Hamishehkar), AliNokhodchi@lupin.com, a.nokhodchi@sussex.ac.uk (A. Nokhodchi).
[1] These authors made equal contributions to this research and should be considered as co-first authors.

https://doi.org/10.1016/j.jaerosci.2023.106290
Received 31 July 2023; Received in revised form 7 October 2023; Accepted 21 October 2023
Available online 23 October 2023

effective drug delivery through dry powder inhalers (DPIs), modification of the powder formulation is essential (Chow et al., 2007). Additionally, the selection of a suitable inhaler device (Adams et al., 2012) and patient education (Henning et al., 2010) play crucial roles in ensuring efficient drug delivery to the lungs.

Particle engineering is a critical step in the formulation of inhalable dry powders (Chan, 2008; Chew & Chan, 2002; Claus et al., 2014; Crowder et al., 2002; Weers & Miller, 2015; Yaqoubi et al., 2021). Parameters such as particle geometric diameter, density, and shape factor determine the aerodynamic diameter of particles, which should be less than 5 μm to facilitate effective respiratory delivery of the drug formulation (Chen et al., 2016). Having a reliable particle engineering technique that can produce particles with modified aerodynamic properties is advantageous and imperative for inhaled formulations.

Ultrasonic spray pyrolysis is a technique that involves introducing a solution of interest into a chamber in contact with an ultrasound bath, which atomizes the solution into micron or nano-sized droplets. A gas flow carries the atomized droplets into a heated chamber where the solvent evaporates, and the dried particles are collected using an electrostatic precipitator (Ardekani et al., 2019) (Fig. 1). This method enables the production of particles with controlled and uniform morphologies (Gürmen et al., 2006; Tsai et al., 2004). Ultrasonic spray pyrolysis offers several advantages, including simplicity, cost-effectiveness, compatibility with various solvent systems, and the ability to manufacture particles with the desired size, shape, density, and porosity without the need for surfactants or stabilizers (Perednis, 2003). Compared to conventional particle engineering methods like spray drying and milling, this system provides better control over particle size and morphology uniformity (Abraham et al., 2023; Majerič et al., 2019). While ultrasonic spray pyrolysis is commonly employed in material engineering (Ardekani et al., 2019) its application in formulating pharmaceutical formulations has not been extensively explored.

In the current study, salbutamol sulfate was used as a model drug. Several studies have utilized various particle engineering techniques to prepare adjustable-sized and morphologically diverse salbutamol sulfate particles. Spray drying has been extensively investigated as a promising method for producing DPI formulations (Corrigan et al., 2006; Li et al., 2017; Littringer et al., 2013). Other studies have also explored the impact of carrier morphology on the aerosol performance of salbutamol sulfate (Kaialy et al., 2011, 2012a, 2012b; Mönckedieck et al., 2017).

The aim of the current study was to explore and employ a modified version of the ultrasonic spray pyrolysis technique to produce an inhalable powder of salbutamol sulfate. In this regard, an aqueous solution of salbutamol sulfate was subjected to ultrasonic nebulization and subsequently dried using a hot air flow. The morphological and solid-state characteristics of the resulting formulation were investigated using SEM, DSC, and XRD methods. The aerosolization behavior of the engineered salbutamol sulfate dry powder inhaler

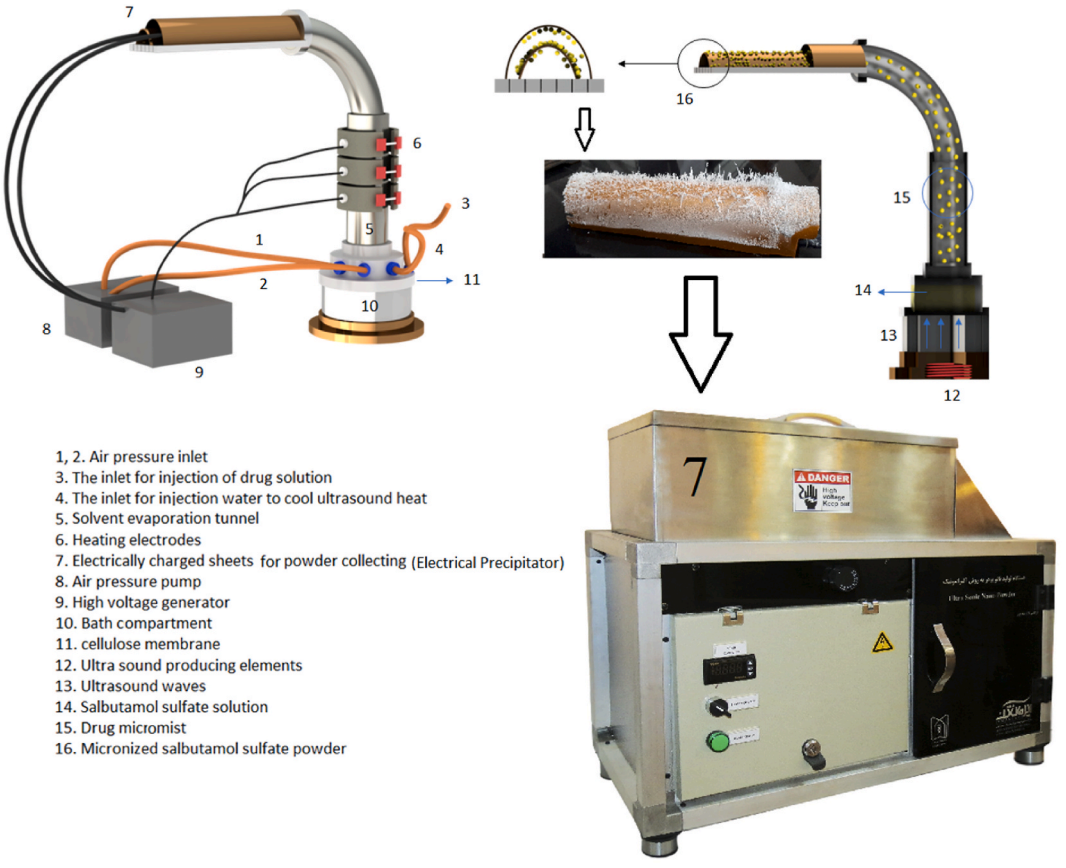

Fig. 1. A schematic illustration of ultrasonic spray pyrolysis.

(DPI) formulation, in which it was mixed with inhalation-grade lactose, was compared with that of a commercial DPI formulation of the drug.

2. Materials and methods

2.1. Materials

Salbutamol sulfate was obtained from RAHA Pharmaceutical (Isfahan, Iran). Ethanol was purchased from JATA (Arak, Iran). Methanol and acetonitrile were provided by Duksan (Ansan, Korea). Lactohale® (LH 200) and 1-heptane sulfonic acid sodium were supplied by DFE PHARMA (Goch, Germany) and Acros Organic (Geel, Belgium), respectively.

2.2. Preparation of salbutamol sulfate powder using ultrasonic atomizer procedure

Salbutamol sulfate (5 g) was dispersed in 50 mL of distilled water (DW) using a magnetic stirrer operating at 200 rpm at room temperature. The solution was stirred until a clear solution was obtained. The clear solution was then injected in several steps into a 20 mL solution reservoir (Fig. 1) in contact with an ultrasonic bath (Irman Tec Sepahan, Iran). The solution was atomized into micronized droplets through ultrasonic nebulization using an ultrasound frequency of approximately 1.7 MHz. The micronized droplets underwent evaporation of the solvent as they passed through a hot air tunnel (Fig. 1, part 5) maintained at a temperature of 170 °C ± 4 °C. After the solvent evaporated, the micronized drug particles were collected on an electrical precipitator with an electrostatic voltage of 20 KV and immediately transferred to a desiccator. The samples were kept inside the desiccator at room temperature for about 2–3 days until further assessments. The experiments were performed in triplicate and the yield of the process was calculated as the percentage ratio between the weight mass of the final engineered product to the mass of the raw drug in the feed solution. The yield was found to be 50 ± 3% (n = 3).

2.3. Scanning Electron Microscopy (SEM)

The morphological topographies of the engineered salbutamol were inspected using a scanning electron microscope (LEO1430 VP, LEO, UK & Germany). An electron beam of 15 kV was utilized for imaging. Prior to imaging, all samples were sputter coated with gold using a desktop sputter coater (DST1 model, Nanostructured Coating Co., Tehran, Iran).

2.4. DSC studies

The thermal pattern of the salbutamol powder was analyzed using a differential scanning calorimeter (DSC-60, Shimadzu, Kyoto, Japan). A precise amount of 2 mg of the engineered drug powder was weighed and placed in a sealed DSC pan. An aluminum oxide-filled DSC pan served as the reference. The heating process was conducted in the temperature range of 20–300 °C at a scanning rate of 10 °C/min. The enthalpy changes of the specimens were analyzed using the provided TA-60WS software (version 1.51).

2.5. X-ray diffraction (XRD)

The crystallographic features of the engineered salbutamol powder were analyzed using a Siemens diffractometer (XRD, D500, Siemens, Karlsruhe, Germany). The diffractogram was obtained by scanning over the rage of 4°–50° (2θ) with a scanning rate of 2°/min.

2.6. Preparation of salbutamol sulfate-carrier blends

The obtained salbutamol sulfate powder was mixed with a lactose carrier (Lactohale®, LH 200, DFE Pharma GmbH & Co. Germany) at a ratio of 1–67.5% w/w using a turbo-mixer (Amin Asia Fannavar Pars, Iran). The trituration method was employed to ensure a uniform mixture of the powders. Each trituration step lasted for 3 min at a speed of 30 rpm. A final blending step of 30 min at 50 rpm was performed to ensure the uniformity of the powder blend.

To assess the homogeneity of salbutamol sulfate in the drug-carrier blends, 10 random samples weighing 10 mg each were taken from different parts of the powder bed and dissolved in 10 ml of distilled water (DW). The samples were then analyzed to measure the drug content.

2.7. In vitro aerosolization assessment

The in vitro aerosolization pattern of the engineered particles was assessed using a next-generation impactor (NGI) equipped with a pre-separator and USP induction port (Nottingham, Copley, UK), following the previously described method (Yaqoubi et al., 2020). Size 3 hard gelatin capsules (Iran gelatin, Iran) filled with 20 mg of the drug-carrier mixture were placed in an Aerolizer® device.

To reduce particle bouncing, the collecting cups were coated with a solution of Tween 80 in ethanol (1% w/v) before the experiments. A flow rate of 60 L/min, was provided by a pump (HCP5, Copley, UK) and controlled using TPK2000 (Copley, Nottingham, UK). The flow rate was measured using a flow meter (Copley, Nottingham, DFM2000, Copley, UK). The flow rate generated a pressure

drop of 4 KPa across the inhaler device. The run time for each actuation was set to 4 s.

The throat and pre-separator of the NGI were rinsed with 15 ml and 35 ml of distilled water (DW), respectively. The Aerolizer®, mouthpiece adaptor, seven collection cups, and micro-orifice collector (MOC) were rinsed with 10 ml of DW. The solutions obtained from rinsing were analyzed using HPLC to determine the drug concentration in each stage.

Fine particle dose (FPD), is generally defined as the cumulative mass of the drug particles with an aerodynamic diameter below 5 μm. Fine particle fraction (FPF) is the fraction (%) of the particles with an aerodynamic diameter below 5 μm that possesses the potential to be sufficiently small to enter the lungs, thereby enabling it to exert a clinical effect. Mass median aerodynamic diameter (MMAD) denotes the size at which 50% of the aerosol particles, by mass, are larger, and the remaining 50% are smaller. This parameter is significant in characterizing the particle size distribution of aerosols, as it provides a central point of reference for understanding the size range of the particles. The geometric standard deviation (GSD) represents the spread of particle sizes on either side of the MMAD, which shows the dispersion degree of the particles in the DPI formulation. All the mentioned parameters were calculated using Copley Inhaler Testing Data Analysis Software (CITDAS, version 3.10, Copley, UK).

2.8. High performance liquid chromatography

For the quantification of salbutamol sulfate in the samples during the homogeneity and deposition studies, an HPLC system from Knauer (Germany) was utilized. The system comprised a model 1000 HPLC pump, a K2600 UV detector, and a 20 μL Knauer loop injector.

To perform the analysis, a Knauer C18 column with dimensions of 25 cm × 46 i.d and a particle size of 5 μm was used as the stationary phase. The mobile phase consisted of a mixture of methanol and a 0.25% (w/v) aqueous solution of 1-heptane sulfonic acid sodium in a ratio of 45:55 (v/v). The flow rate of the mobile phase was set at 1 mL/min.

Detection of the drug was conducted at a wavelength of 200 nm, and the retention time of salbutamol sulfate was approximately 3.5 min. The method exhibited a linear calibration range for salbutamol sulfate with an R square value of 0.9999 ± 0.0001. The LOD and LOQ values were 0.015 and 0.047 μg/mL, respectively. The precision values were between 3.014 and 7.124%, the accuracy was between 0.343 and 9.065%. Each sample was analyzed three times at room temperature.

3. Results and discussion

3.1. Particle size and morphology

Fig. 2 shows the morphological attributes of the engineered salbutamol sulfate particles. The analysis of the particle size of the engineered salbutamol sulfate was conducted through the examination of SEM (Scanning Electron Microscopy) images. This involved measuring the Feret diameter of the obtained particles, which resulted in the determination of key size percentiles. Specifically, the D90, D10, and D50 values were found to be 2.76 μm, 1.61 μm, and 2.11 μm, respectively. Notably, the small span value of 0.55

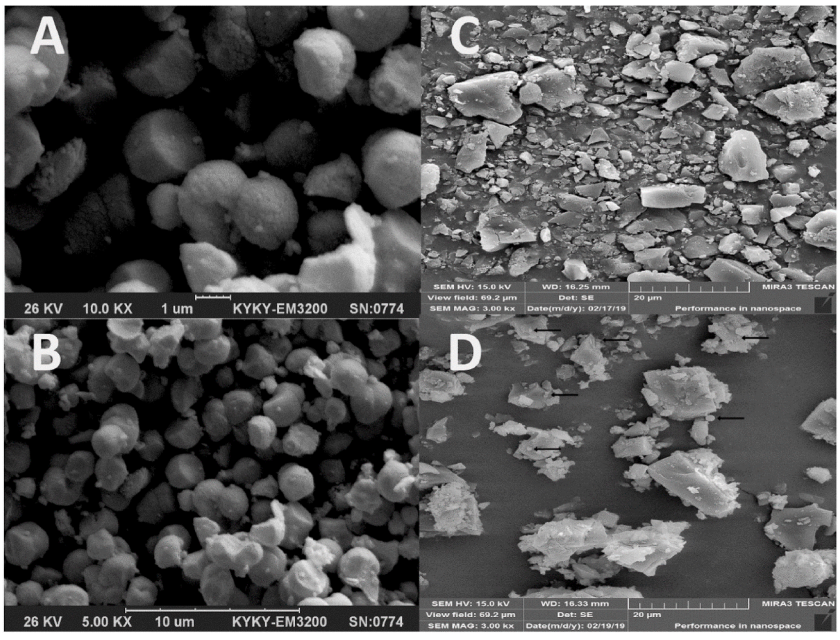

Fig. 2. SEM images of (A and B) salbutamol sulfate dry powder inhalers prepared by ultrasonic atomizer, (C) Lactohale®, (D) engineered salbutamol sufate mixed with Lactohale®. The arrows indicate salbutamol particles attached to the Lactohale®.

highlights the narrow particle size distribution achieved in this study. This observation underscores the remarkable uniformity in both size and shape among the engineered particles, which is a significant factor in their potential applications.

This characteristic is a key advantage offered by the ultrasonic spray pyrolysis method, as it ensures consistent particle properties throughout the formulation (Gürmen et al., 2006; Tsai et al., 2004; Wang et al., 2008).

The uniformity of the produced powder holds significant value in various drug delivery applications, particularly in pulmonary drug delivery (Chow et al., 2007). Furthermore, the particles obtained through this technique exhibit a desirable level of sphericity and regularity, which are highly sought-after qualities in particle engineering methods aimed at generating spherical or regularly shaped particles (Gürmen et al., 2006; Košević et al., 2019; Lee & Park, 1993; Milošević et al., 1994; Song et al., 2004). The shape of the particles plays a critical role in determining the aerosolization efficiency of dry powder inhaler (DPI) formulations (Adams et al., 2012; Yaqoubi et al., 2021). While some studies highlight the advantages of elongated particles in terms of airborne characteristics (Hamishehkar et al., 2010; Kaialy et al., 2010), others underscore the superior flowability and reduced particle-particle interactions of spherical particles (Carrigy et al., 2019; Momin et al., 2019). The findings from this study align with these perspectives, as the engineered salbutamol sulfate particles demonstrate acceptable aerosolization performance. Notably, Fig. 2 reveals that the mean particle size falls within the range of 2–3 μm, which is considered an optimal size range for efficient pulmonary drug delivery (De Boer et al., 2015).

These findings demonstrate the potential of the ultrasonic spray pyrolysis method for formulating inhalable dry powder formulations of drugs. Further studies and development are warranted to explore the full potential of this particle engineering technique in the field of drug delivery.

3.2. Solid state characterizations

In Fig. 3, the differential scanning calorimetry (DSC) traces of both the initial material (Green difractogram) and the ultrasonic spray pyrolyzed salbutamol sulfate (Red difractogram) are presented, revealing distinct thermal behavior and further elucidating the transformation of the drug during the particle engineering process. The DSC trace of the starting material clearly exhibits characteristic features associated with its crystalline nature, prominently shown by an endothermic peak observed at approximately 200 °C. The onset of this peak is detected at 188 °C, with its maximum intensity occurring around 197 °C, aligning with the known melting point of salbutamol sulfate as reported by Fattah et al. (Fattah et al., 1998).

A remarkable disparity is observed between the thermograms of the two formulations, specifically in terms of peak onset, endset, and the overall area under the curve. These differences can be attributed to the transformative effect of the particle engineering process on the crystallinity of salbutamol sulfate. Previous studies by Kong and Hay (Kong & Hay, 2002, 2003) have highlighted the phenomenon of amorphization during the particle engineering procedure, shedding light on the observed variations in the DSC traces. The most significant change is the shift of the endothermic peak to a lower temperature, indicating a modification in the thermal properties of salbutamol sulfate due to the amorphization process. Additionally, there is a remarkable reduction in enthalpy, with the treated drug displaying a significantly lower value of 2.65 J/g compared to the unprocessed material, which had an enthalpy of 182.71 J/g.

These findings provide compelling evidence for the alteration in the crystallinity of salbutamol sulfate-induced by ultrasonic spray pyrolysis, further confirming the capability of this technique in producing amorphous materials, as also supported by studies conducted by Ye et al. and Liu et al. (Liu et al., 2020; Ye et al., 2017).

Fig. 4 represents the X-ray diffraction (XRD) patterns of salbutamol sulfate before and after the ultrasonic atomization process,

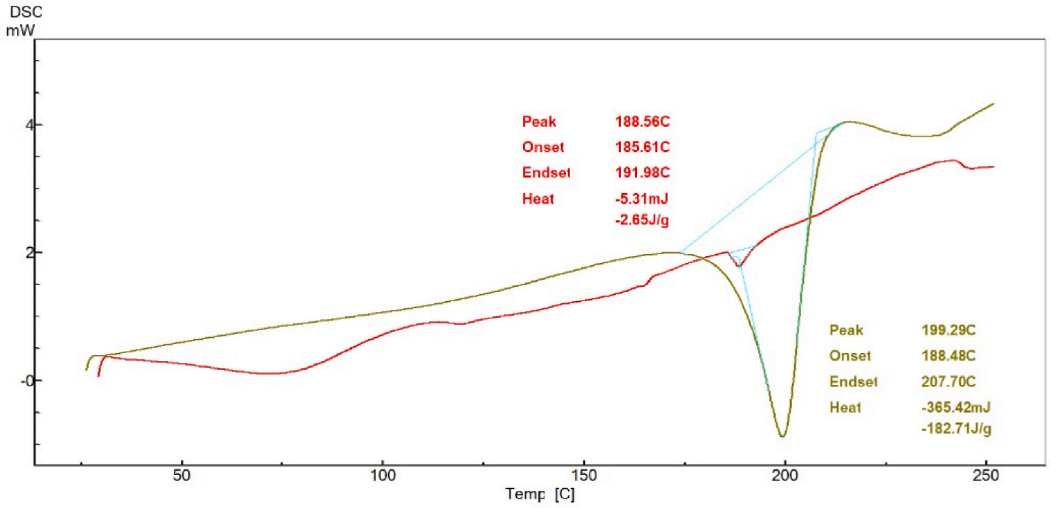

Fig. 3. DSC thermograms of salbutamol sulfate. (Green) Untreated salbutamol sulfate. (Red) Engineered salbutamol sulfate. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

offering valuable insights into the structural changes induced by this particle engineering technique. In Fig. 4a, the XRD pattern of the raw salbutamol sulfate clearly exhibits sharp and well-defined peaks at 11° and 23° (2θ), providing unequivocal evidence of its crystalline nature. Conversely, Fig. 4b showcases the XRD pattern of the engineered powder, revealing a distinctive absence of sharp peaks, indicative of the transformed amorphous state of the drug. This transformation can be ascribed to the high-temperature airflow generated during the ultrasonic spray pyrolysis process, as reported in prior studies (Liu et al., 2020; Ye et al., 2017). The deliberate amorphization of the drug particles through this method enhances the prospects of producing inhalable drug powders with improved properties.

An intriguing aspect of amorphous materials is their lower density in comparison to their crystalline counterparts, as extensively studied by other researchers (Einfalt et al., 2013; Kho & Hadinoto, 2013; Lu et al., 2019). The lower density of the amorphous form offers distinct advantages in formulating inhalable drug products, as it facilitates easier dispersibility and aerosolization. This advantageous characteristic holds significant promise for enhancing the drug's delivery to the targeted respiratory region. However, it is crucial to acknowledge the inherent challenge of lower stability associated with amorphous materials, which can impact the long-term performance and shelf-life of the final drug product. Formulators need to carefully address this stability concern during the drug development process.

To assess the long-term stability of the amorphous salbutamol sulfate formulation, the XRD results of the engineered powder were reevaluated after a 6-month stability testing period, as depicted in Fig. 4c. Encouragingly, the diffractogram of the micronized drug after this extended storage period still exhibits an amorphous pattern, demonstrating the sustained stability of the amorphous state under ambient conditions.

This stability observation is of significant importance for the practical application of the ultrasonic spray pyrolysis method in preparing inhalable drug formulations. The ability to maintain the amorphous state over an extended period opens up new possibilities for the development of stable and effective pulmonary drug delivery systems.

In conclusion, Fig. 4 highlights the successful transformation of crystalline salbutamol sulfate particles into the amorphous state using ultrasonic spray pyrolysis. This structural modification significantly impacts the density and stability of the engineered particles, offering distinct advantages for pulmonary drug delivery. The observed stability of the amorphous state after 6 months of storage underscores the potential of this particle engineering technique as a promising approach to create inhalable drug powders with enhanced properties and performance.

3.3. Homogeneity of drug content

The blended formulation demonstrated an impressive level of uniformity in drug content, as evidenced by the coefficient of variation (CV%) calculated for ten randomly selected samples, all of which yielded values of less than 10%. This outcome signifies the reliability and reproducibility of the blending and sampling procedures employed in this study.

3.4. In vitro deposition profile

Fig. 5 and Table 1 present the in vitro aerosolization performance of the engineered formulation of salbutamol sulfate (aerosolized using Aerolizer®) compared to the commercial form (Ventolin Accuhaler®). The figure illustrates the percentage of drug deposited in each collecting cup of the Next Generation Impactor (NGI). Although the amount of drug remaining in the Ventolin Accuhaler® device was not assessed, it was determined to be very low (less than 2%) for the engineered formulation.

Regarding deposition, a higher percentage of the drug was deposited in the USP induction port (the throat) for the engineered

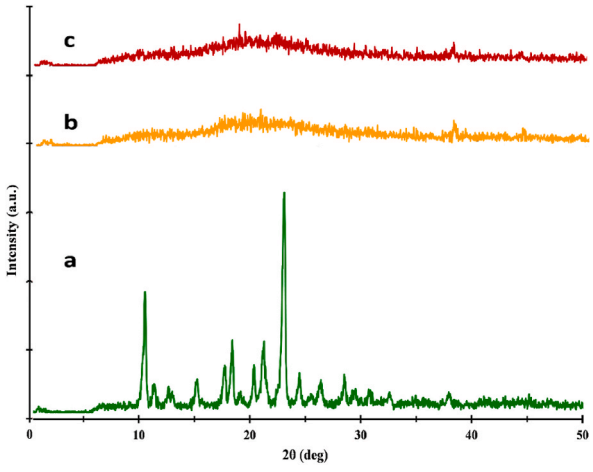

Fig. 4. XRD diffractograms of (a) salbutamol sulfate, (b) engineered salbutamol sulfate and (c) engineered salbutamol sulfate after 6 months of storage at ambient conditions.

formulation (19%) in comparison to the commercial formulation (11%). However, the drug deposited in the preseparator was lower for the engineered formulation (24%) compared to Ventolin® (50%). The total percentage of non-respirable drug particles in the throat and preseparator, representing larger particles, was significantly lower for the engineered formulation (43%) compared to the commercial form (61%). These findings suggest that the engineered formulation has a lower proportion of non-respirable particles.

Furthermore, a significant number of particles landed on stages 2–5, which correspond to the respirable size range of 1–5 μm, for both formulations. This indicates that both formulations are suitable for inhalation approaches. These results align with the in vitro aerosolization performance assessment, where the mass median aerodynamic diameter (MMAD) of the particles was $\leq$5 μm for both formulations. The fine particle fraction (FPF) values were 25% for the engineered formulation and 33% for Ventolin®. Although the difference in FPF values is statistically significant, it can be inferred that the aerosolization efficiency of the engineered formulation is comparable to that of Ventolin®.

It is estimated that for a DPI formulation, a mere 10–15% of the drug reaches the deep lung, while 20% deposits in the throat area, and a significant portion of 65% attaches firmly to the carrier without releasing the drug particles (Lechanteur & Evrard, 2020). In light of this, it is noteworthy that the engineered formulation in this study demonstrates a fine particle fraction (FPF) value of 25%, surpassing the typical FPF of around 15% observed in commercially available dry powder inhaler (DPI) products (Table 1). This higher FPF value indicates improved efficiency in delivering drug particles to the desired site of action and suggests that the engineered formulation exhibits acceptable aerosolization performance.

Although the application of hot air for particle engineering is the accepted methodology in the pharmaceutical industry, their use is not amenable to heat-sensitive drugs. Therefore, introducing hot air-based particle engineering approaches such as ultrasonic spray pyrolysis, in which the time for heat exposure is controlled, will be of great interest. Ultrasonic spray pyrolysis offers notable advantages over conventional spray drying processes in which the nebulized drug solution is exposed to a high temperature just inside a short hot air tunnel with a length of about 30 cm. Due to the limited exposure to the hot temperature, it is likely for a drug to feel a lower temperature than that provided by the system, indicating its potential use for heat-sensitive drugs. Despite these advantages, it is important to note that the claimed benefits of ultrasonic spray pyrolysis for heat-sensitive drugs require further validation through stability assessments. These assessments are essential to confirm the hypothesis that this methodology indeed offers a safer and more effective solution for the particle engineering of such pharmaceuticals. Furthermore, compared to spray drying which utilizes a downdraft flow path, the flow path for ultrasonic spray pyrolysis is updraft. This difference provides an ability for ultrasonic spray pyrolysis to avoid the entering of large and wet particles into the collection chamber. Additionally, this particle engineering method proves suitable for highly potent drugs with low batch production capacity, which may not be well-suited for milling techniques like jet milling. Moreover, the closed system utilized in this method provides added benefits for the particle engineering of high OEL (occupational exposure limit) drugs such as corticosteroids, ensuring a controlled and safe environment.

It is important to acknowledge that this study represents an initial investigation into the technology, and further optimization is necessary to achieve even more desirable FPF values. Nonetheless, the preliminary results and advantages demonstrated by the

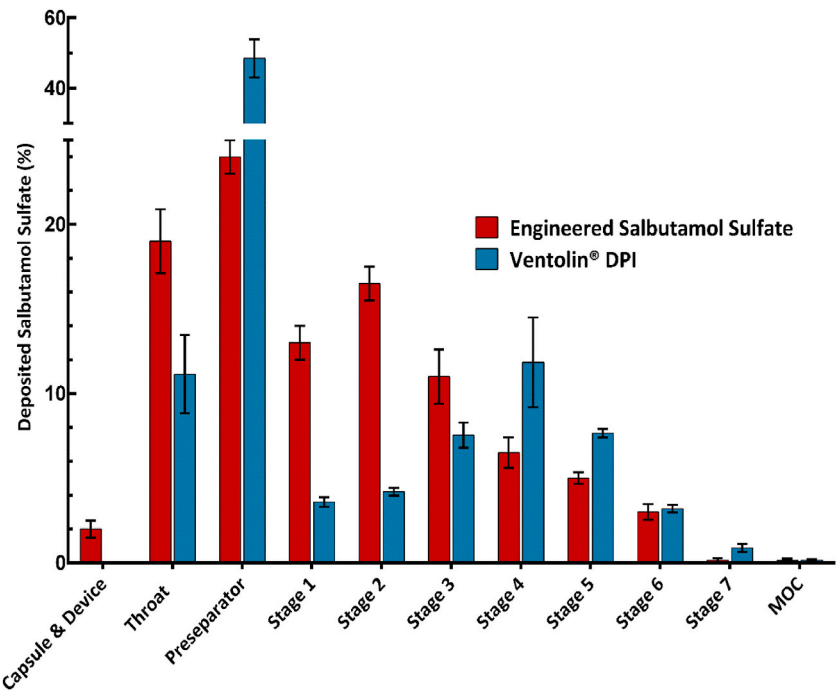

Fig. 5. In vitro deposition pattern of salbutamol sulfate in next generation impactor (NGI). Engineered Salbutamol Sulfate was blended with Lactohale® and aerosolized by an Aerolizer®. Commercial DPI form of salbutamol sulfate (Ventolin®) was aerosolized by an Accuhaler®.

Table 1
Inhalation characteristics of salbutamol sulfate dry powder inhaler prepared in this study with ultrasonic atomizer compared to commercial form. Engineered Salbutamol Sulfate was blended with Lactohale® and aerosolized by an Aerolizer®. Commercial DPI form of salbutamol sulfate (Ventolin®) was aerosolized by an Accuhaler®.

	Engineered Formulation	Ventolin Accuhaler®
FPD[a] (μg)	58 ± 4	72 ± 6
FPF[b] (%)	25 ± 2	33 ± 3
MMAD[c] (μm)	5 ± 0.05	2.36 ± 0.08
GSD[d]	1.93 ± 0.01	2.30 ± 0.13

[a] Fine Particle Dose (FPD).
[b] Fine Particle Fraction (FPF).
[c] Mass Median Aerodynamic Diameter (MMAD).
[d] Geometric Standard Deviation (GSD).

particle engineering method offer promising prospects for the development of inhalable drug formulations with enhanced aerosolization performance and stability.

4. Conclusion

Ultrasonic spray pyrolysis is being used for non-pharmaceutical purposes. The current study demonstrates the potential of ultrasonic spray pyrolysis as an innovative approach for producing inhalable drug powders with improved characteristics. Further research and development in this area will contribute to advancing the field of pulmonary drug delivery and enhancing the therapeutic outcomes for patients. Here, this technique successfully generated controlled-size and homogeneous micron-sized dry powder inhaler (DPI) formulations of salbutamol sulfate particles. The resulting particles exhibit desirable aerosolization performance, characterized by size distribution within the respirable range and modified shape and surface morphologies. However, it is essential to continue refining and validating ultrasonic spray pyrolysis such as solution concentration, ultrasonic aerosolization parameters, outlet conditions, and air temperature to optimize its performance and establish its reliability in the field of pulmonary drug delivery.

Comparative studies with other methods such as spray drying would provide valuable insights into the advantages and limitations of ultrasonic spray pyrolysis.

Funding

This study was financially supported by Tabriz University of Medical Sciences, Tabriz, Iran (Grant No. 59677).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgment

The authors would like to appreciate the cooperation of the Clinical Research Development Unit of Imam Reza General Hospital, Tabriz, Iran in conducting this research.

References

Abraham, P., Shaji, S., Avellaneda, D. A., Aguilar-Martínez, J. A., & Krishnan, B. (2023). (002) oriented ZnO and ZnO: S thin films by direct ultrasonic spray pyrolysis: A comparative analysis of structure, morphology and physical properties. *Materials Today Communications, 35*, Article 105909. https://doi.org/10.1016/j.mtcomm.2023.105909

Adams, W. P., Lee, S. L., Plourde, R., Lionberger, R. A., Bertha, C. M., Doub, W. H., … Hickey, A. J. (2012). Effects of device and formulation on in vitro performance of dry powder inhalers. *The AAPS Journal, 14*, 400–409. https://doi.org/10.1208/s12248-012-9352-7

Ardekani, S. R., Aghdam, A. S. R., Nazari, M., Bayat, A., Yazdani, E., & Saievar-Iranizad, E. (2019). A comprehensive review on ultrasonic spray pyrolysis technique: Mechanism, main parameters and applications in condensed matter. *Journal of Analytical and Applied Pyrolysis, 141*, Article 104631. https://doi.org/10.1016/j.jaap.2019.104631

Carrigy, N. B., Ordoubadi, M., Liu, Y., Melhem, O., Barona, D., Wang, H., … Vehring, R. (2019). Amorphous pullulan trehalose microparticle platform for respiratory delivery. *International Journal of Pharmaceutics, 563*, 156–168. https://doi.org/10.1016/j.ijpharm.2019.04.004

Chan, H. K. (2008). What is the role of particle morphology in pharmaceutical powder aerosols? *Expert Opinion on Drug Delivery, 5*(8), 909–914. https://doi.org/10.1517/17425247.5.8.909

Chen, L., Okuda, T., Lu, X. Y., & Chan, H. K. (2016). Amorphous powders for inhalation drug delivery. *Advanced Drug Delivery Reviews, 100*, 102–115. https://doi.org/10.1016/j.addr.2016.01.002

Chew, N. Y., & Chan, H. K. (2002). The role of particle properties in pharmaceutical powder inhalation formulations. *Journal of Aerosol Medicine, 15*(3), 325–330. https://doi.org/10.1089/089426802760292672

Chow, A. H., Tong, H. H., Chattopadhyay, P., & Shekunov, B. Y. (2007). Particle engineering for pulmonary drug delivery. *Pharmaceutical Research, 24*, 411–437. https://doi.org/10.1007/s11095-006-9174-3

Claus, S., Weiler, C., Schiewe, J., & Friess, W. (2014). How can we bring high drug doses to the lung? *European Journal of Pharmaceutics and Biopharmaceutics, 86*(1), 1–6. https://doi.org/10.1016/j.ejpb.2013.11.005

Corrigan, D. O., Corrigan, O. I., & Healy, A. M. (2006). Physicochemical and in vitro deposition properties of salbutamol sulphate/ipratropium bromide and salbutamol sulphate/excipient spray dried mixtures for use in dry powder inhalers. *International Journal of Pharmaceutics, 322*(1–2), 22–30. https://doi.org/10.1016/j.ijpharm.2006.05.022

Crowder, T. M., Rosati, J. A., Schroeter, J. D., Hickey, A. J., & Martonen, T. B. (2002). Fundamental effects of particle morphology on lung delivery: Predictions of Stokes' law and the particular relevance to dry powder inhaler formulation and development. *Pharmaceutical Research, 19*, 239–245. https://doi.org/10.1023/a:1014426530935

De Boer, A. H., Gjaltema, D., Hagedoorn, P., & Frijlink, H. W. (2015). Can 'extrafine'dry powder aerosols improve lung deposition? *European Journal of Pharmaceutics and Biopharmaceutics, 96*, 143–151. https://doi.org/10.1016/j.ejpb.2015.07.016

Einfalt, T., Planinšek, O., & Hrovat, K. (2013). Methods of amorphization and investigation of the amorphous state. *Acta Pharmaceutica, 63*(3), 305–334. https://doi.org/10.2478/acph-2013-0026

ElKasabgy, N. A., Adel, I. M., & Elmeligy, M. F. (2020). Respiratory tract: Structure and attractions for drug delivery using dry powder inhalers. *AAPS PharmSciTech, 21*, 1–14. https://doi.org/10.1208/s12249-020-01757-2

Fattah, E. A. E., Grant, D. J. W., Gabr, K. E., & Meshali, M. M. (1998). Physical characteristics and release behavior of salbutamol sulfate beads prepared with different ionic polysaccharides. *Drug Development and Industrial Pharmacy, 24*(6), 541–547. https://doi.org/10.3109/03639049809085655

Gürmen, S., Stopić, S., & Friedrich, B. (2006). Synthesis of nanosized spherical cobalt powder by ultrasonic spray pyrolysis. *Materials Research Bulletin, 41*(10), 1882–1890. https://doi.org/10.1016/j.materresbull.2006.03.006

Hamishehkar, H., Emami, J., Najafabadi, A. R., Gilani, K., Minaiyan, M., Mahdavi, H., & Nokhodchi, A. (2010). Effect of carrier morphology and surface characteristics on the development of respirable PLGA microcapsules for sustained-release pulmonary delivery of insulin. *International Journal of Pharmaceutics, 389*(1–2), 74–85. https://doi.org/10.1016/j.ijpharm.2010.01.021

Henning, A., Hein, S., Schneider, M., Bur, M., & Lehr, C. M. (2010). Pulmonary drug delivery: Medicines for inhalation. *Drug Delivery*, 171–192. https://doi.org/10.1007/978-3-642-00477-3_6

Kaialy, W., Alhalaweh, A., Velaga, S. P., & Nokhodchi, A. (2011). Effect of carrier particle shape on dry powder inhaler performance. *International Journal of Pharmaceutics, 421*(1), 12–23. https://doi.org/10.1016/j.ijpharm.2011.09.010

Kaialy, W., Martin, G. P., Larhrib, H., Ticehurst, M. D., Kolosionek, E., & Nokhodchi, A. (2012). The influence of physical properties and morphology of crystallised lactose on delivery of salbutamol sulphate from dry powder inhalers. *Colloids and Surfaces B: Biointerfaces, 89*, 29–39. https://doi.org/10.1016/j.colsurfb.2011.08.019

Kaialy, W., Momin, M. N., Ticehurst, M. D., Murphy, J., & Nokhodchi, A. (2010). Engineered mannitol as an alternative carrier to enhance deep lung penetration of salbutamol sulphate from dry powder inhaler. *Colloids and Surfaces B: Biointerfaces, 79*(2), 345–356. https://doi.org/10.1016/j.colsurfb.2010.04.016

Kaialy, W., Ticehurst, M., & Nokhodchi, A. (2012). Dry powder inhalers: Mechanistic evaluation of lactose formulations containing salbutamol sulphate. *International Journal of Pharmaceutics, 423*(2), 184–194. https://doi.org/10.1016/j.ijpharm.2011.12.018

Kho, K., & Hadinoto, K. (2013). Dry powder inhaler delivery of amorphous drug nanoparticles: Effects of the lactose carrier particle shape and size. *Powder Technology, 233*, 303–311. https://doi.org/10.1016/j.powtec.2012.09.023

Kong, Y., & Hay, J. N. (2002). The measurement of the crystallinity of polymers by DSC. *Polymer, 43*(14), 3873–3878. https://doi.org/10.1016/S0032-3861(02)00235-5

Kong, Y., & Hay, J. N. (2003). The enthalpy of fusion and degree of crystallinity of polymers as measured by DSC. *European Polymer Journal, 39*(8), 1721–1727. https://doi.org/10.1016/S0014-3057(03)00054-5

Košević, M. G., Zarić, M. M., Stopić, S. R., Stevanović, J. S., Weirich, T. E., Friedrich, B. G., & Panić, V. V. (2019). Structural and electrochemical properties of nesting and core/shell Pt/TiO2 spherical particles synthesized by ultrasonic spray pyrolysis. *Metals, 10*(1), 11. https://doi.org/10.3390/met10010011

Lechanteur, A., & Evrard, B. (2020). Influence of composition and spray-drying process parameters on carrier-free DPI properties and behaviors in the lung: A review. *Pharmaceutics, 12*(1), 55. https://doi.org/10.3390/pharmaceutics12010055

Lee, J. H., & Park, S. J. (1993). Preparation of spherical SnO2 powders by ultrasonic spray pyrolysis. *Journal of the American Ceramic Society, 76*(3), 777–780. https://doi.org/10.1111/j.1151-2916.1993.tb03678.x

Li, L., Leung, S. S. Y., Gengenbach, T., Yu, J., Gao, G. F., Tang, P., … Chan, H. K. (2017). Investigation of L-leucine in reducing the moisture-induced deterioration of spray-dried salbutamol sulfate power for inhalation. *International Journal of Pharmaceutics, 530*(1–2), 30–39. https://doi.org/10.1016/j.ijpharm.2017.07.033

Littringer, E. M., Zellnitz, S., Hammernik, K., Adamer, V., Friedl, H., & Urbanetz, N. A. (2013). Spray drying of aqueous salbutamol sulfate solutions using the nano spray dryer B-90—the impact of process parameters on particle size. *Drying Technology, 31*(12), 1346–1353. https://doi.org/10.1080/07373937.2013.793701

Liu, H. Y., Hsu, W. C., Chen, J. H., Hsu, P. H., & Lee, C. S. (2020). Amorphous ITZO thin-film transistors by using ultrasonic spray pyrolysis deposition. *IEEE Transactions on Electron Devices, 67*(3), 1009–1013. https://doi.org/10.1109/TED.2020.2965949

Lu, W., Rades, T., Rantanen, J., & Yang, M. (2019). Inhalable co-amorphous budesonide-arginine dry powders prepared by spray drying. *International Journal of Pharmaceutics, 565*, 1–8. https://doi.org/10.1016/j.ijpharm.2019.04.036

Majerič, P., Feizpour, D., Friedrich, B., Jelen, Ž., Anžel, I., & Rudolf, R. (2019). Morphology of composite Fe@ Au submicron particles, produced with ultrasonic spray pyrolysis and potential for synthesis of Fe@ Au core–shell particles. *Materials, 12*(20), 3326. https://doi.org/10.3390/ma12203326

Milošević, O., Jordović, B., & Uskoković, D. (1994). Preparation of fine spherical ZnO powders by an ultrasonic spray pyrolysis method. *Materials Letters, 19*(3–4), 165–170. https://doi.org/10.1016/0167-577X(94)90063-9

Momin, M. A., Sinha, S., Tucker, I. G., & Das, S. C. (2019). Carrier-free combination dry powder inhaler formulation of ethionamide and moxifloxacin for treating drug-resistant tuberculosis. *Drug Development and Industrial Pharmacy, 45*(8), 1321–1331. https://doi.org/10.1080/03639045.2019.1609494

Mönckedieck, M., Kamplade, J., Fakner, P., Urbanetz, N. A., Walzel, P., Steckel, H., & Scherließ, R. (2017). Dry powder inhaler performance of spray dried mannitol with tailored surface morphologies as carrier and salbutamol sulphate. *International Journal of Pharmaceutics, 524*(1–2), 351–363. https://doi.org/10.1016/j.ijpharm.2017.03.055

Perednis, D. (2003). *Thin film deposition by spray pyrolysis and the application in solid oxide fuel cells (Doctoral dissertation, ETH Zurich)*.

Song, Y. L., Tsai, S. C., Chen, C. Y., Tseng, T. K., Tsai, C. S., Chen, J. W., & Yao, Y. D. (2004). Ultrasonic spray pyrolysis for synthesis of spherical zirconia particles. *Journal of the American Ceramic Society, 87*(10), 1864–1871. https://doi.org/10.1111/j.1151-2916.2004.tb06332.x

Son, Y. J., & McConville, J. T. (2008). Advancements in dry powder delivery to the lung. *Drug Development and Industrial Pharmacy, 34*(9), 948–959. https://doi.org/10.1080/03639040802235902

Tsai, S. C., Song, Y. L., Tsai, C. S., Yang, C. C., Chiu, W. Y., & Lin, H. M. (2004). Ultrasonic spray pyrolysis for nanoparticles synthesis. *Journal of Materials Science, 39*, 3647–3657. https://doi.org/10.1023/B:JMSC.0000030718.76690.11

Wang, W. N., Purwanto, A., Lenggoro, I. W., Okuyama, K., Chang, H., & Jang, H. D. (2008). Investigation on the correlations between droplet and particle size distribution in ultrasonic spray pyrolysis. *Industrial & Engineering Chemistry Research, 47*(5), 1650–1659. https://doi.org/10.1021/ie070821d

Weers, J. G., & Miller, D. P. (2015). Formulation design of dry powders for inhalation. *Journal of Pharmaceutical Sciences, 104*(10), 3259–3288. https://doi.org/10.1002/jps.24574

Yaqoubi, S., Adibkia, K., Nokhodchi, A., Emami, S., Alizadeh, A. A., Hamishehkar, H., & Barzegar-Jalali, M. (2020). Co-electrospraying technology as a novel approach for dry powder inhalation formulation of montelukast and budesonide for pulmonary co-delivery. *International Journal of Pharmaceutics, 591*, Article 119970. https://doi.org/10.1016/j.ijpharm.2020.119970

Yaqoubi, S., Chan, H. K., Nokhodchi, A., Dastmalchi, S., Alizadeh, A. A., Barzegar-Jalali, M., & Hamishehkar, H. (2021). A quantitative approach to predicting lung deposition profiles of pharmaceutical powder aerosols. *International Journal of Pharmaceutics, 602*, Article 120568. https://doi.org/10.1016/j.ijpharm.2021.120568

Ye, Z., Yang, J., Li, B., Shi, L., Ji, H., Song, L., & Xu, H. (2017). Amorphous molybdenum sulfide/carbon nanotubes hybrid nanospheres prepared by ultrasonic spray pyrolysis for electrocatalytic hydrogen evolution. *Small, 13*(21), Article 1700111. https://doi.org/10.1002/smll.201700111

Zhong, H., Chan, G., Hu, Y., Hu, H., & Ouyang, D. (2018). A comprehensive map of FDA-approved pharmaceutical products. *Pharmaceutics, 10*(4), 263. https://doi.org/10.3390/pharmaceutics1004026