

A Modified KinetiSol Process to Produce Dry Powder Blends for Pulmonary Delivery

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Summary

This study introduces powder discharge-based KinetiSol (pKSD) as a novel particle engineering process for manufacturing dry powders suitable for inhalation. pKSD is a KinetiSol-derived method that, through modified parameters, produces powder blends rather than conventional melt agglomerates. KinetiSol technology is a scalable, solvent-free process that is primarily used to produce amorphous solid dispersions. Now, we have adapted KinetiSol, identifying pKSD as a high-energy mixing technique capable of generating nano- and micron-sized particulate aggregates with a higher bulk density, enabling high-dose drug loading. The research focuses on pKSD's potential for improving the solubility of poorly water-soluble drugs; however, a deeper understanding of its influence on excipient morphology and subsequent aerosol performance is required to apply it to pulmonary drug delivery.

In this study, we investigated pKSD's capability to produce powder blends for inhalation using crystalline L-leucine and amorphous cyclodextrins. We evaluated their aerosol performance, bulk densities, and the impact of the pKSD process on particle size and morphology. Results showed that pKSD significantly reduced the particle size of L-Leucine and hydroxypropyl- β -cyclodextrin (HPBCD), leading to an approximately 50% fine particle fraction (FPF), which is comparable to that of commercially approved products. Conversely, sulfobutyl ether- β -cyclodextrin (SBECD) retained its original morphology and size, resulting in a lower FPF (21%). In conclusion, pKSD effectively modifies powder blend characteristics based on excipient properties. Additionally, the higher bulk densities achieved with pKSD, compared to spray-dried formulations, make pKSD a suitable particle engineering approach for targeted high-dose drug delivery to the lungs.

Key Message

KinetiSol, a fusion-based, scalable technology for generating amorphous solid dispersions, has been modified into **powder discharge-based KinetiSol** to produce dry powder blends for inhalation. This approach, not previously applied to pulmonary delivery, effectively alters excipient characteristics, demonstrating significant potential for targeted drug delivery and complementing existing manufacturing methods.

Introduction

Powders for dry powder inhalation made by spray-drying often exhibit characteristics like lower bulk density, which can limit drug loading [1]. To solve this limitation, we developed the powder discharge-based KinetiSol (pKSD) as a novel particle engineering process to manufacture dry powders suitable for pulmonary drug delivery. KinetiSol is a solvent-free, high-shear fusion-based process recognized for manufacturing amorphous solid dispersions [2]. Furthermore, the KinetiSol technology is well-established for its scalability, transitioning from small-scale development to large-scale production, making it an attractive option for pharmaceutical manufacturing [2], [3]. Additionally, KinetiSol has demonstrated to produce homogenous mixtures with as low as 1% drug load [4]. Notably, recent parameter modifications to the KinetiSol process have led to the production of pKSD samples comprising nano- and micron-sized particulate aggregates, which suggests its use for pulmonary drug delivery [5].

This study examines the application of the pKSD method to produce powder blends using both crystalline and amorphous excipients. Jara *et al.* recently reported the use of amorphous excipients to prepare pKSD samples, aiming to increase the solubility of a drug for oral administration; however, inhalation excipients, such as leucine, have not been evaluated. Amorphous and crystalline excipients have distinct physicochemical properties, such as plastic stiffness, which has an impact on particle breakage [6]. When particles undergo mechanical processing, especially due to high-shear methods, particle size and morphology are often altered, which might affect bulk density. Our primary objective was to evaluate the aerosol performance of these pKSD-based powder blends and to analyze the influence of high-shear processing on the final particle size, morphology, and bulk densities of the pKSD powder blends.

Experimental Methods

Powder Discharge-Based KinetiSol Processing (pKSD): Fenbendazole (FBZ) was blended with cyclodextrins (1:2 molar ratio) and 0.5% w/w of magnesium stearate. Then, the powder blend was processed using the pKSD technique in the KinetiSol chamber (KinetiSol research formulator, KBC20, AustinPx, LLC, Georgetown, TX). Hydroxypropyl β cyclodextrin (i.e., Kleptose® HPB, HPBCD) was purchased from Roquette America (Geneva, IL, USA), L-Leucine (Leu, Alphaesar, Fisher Scientific, Pittsburgh, PA, USA), and Captisol® (sulfobutylether- β -cyclodextrin, SBECD) was gifted by Ligand Pharmaceuticals (San Diego, CA, USA). The processing sequence involved an initial blending step at 1000 RPM for 5 seconds, followed by a processing phase at 5000 RPM for 90 seconds. A final, brief processing step at 1000 RPM for 5 seconds was included to minimize dust generation. The leucine blend was prepared with FBZ at 5% w/w and 0.5% w/w of magnesium stearate. The FBZ-Leu powder was blended at 1000 RPM for 5 seconds, following a second phase of processing at 4000 RPM for 30 seconds (second phase), with a final blending step at 1000 RPM for 5 seconds [5].

Scanning Electron Microscopy (SEM): Samples were mounted onto carbon tape affixed to aluminum stubs for morphological analysis. These prepared samples were then sputter-coated with a gold/palladium mixture using an EMS Sputter Coater (Hatfield, PA, USA). Images were captured using an Apreo 2 C LoVac SEM instrument (Waltham, MA, USA).

Particle Size Analysis: The particle size distribution of pKSD-processed samples and individual excipients was determined via laser light diffraction. Measurements were performed using a HELOS/KR system (Sympatec GmbH) equipped with a Rodos dry dispersing system, which operated at a pressure of 4 bar. Data evaluation and analysis were conducted using Windox 5 software.

Aerosol Performance: The in vitro aerosol performance of the pKSD samples was assessed using a Next Generation Impactor (NGI, Copley Scientific, Nottingham, UK). Formulations, consisting of 40 mg of powder loaded into Size 3 HPMC capsules, were aerosolized through a High Resistance RS01 Monodose DPI (Berry Global Healthcare, IN, US) at a flow rate of 60 L/min for 4 seconds, generating a 4 kPa pressure drop. Each experiment was performed in triplicate, with two loaded capsules utilized per NGI run. Particles deposited within the impactor stages were recovered using DMSO. The FPF) was calculated as the percentage of particles with an aerodynamic diameter less than 5 μ m, relative to the measured emitted dose.

Bulk density: Bulk density was determined using a modified USP <616> method, it was adapted due to the low amount of powder available [7]. A specific mass of powder was added to a 5 mL cylinder, and the volume noted. Measurements were performed in triplicate.

Results and Discussion

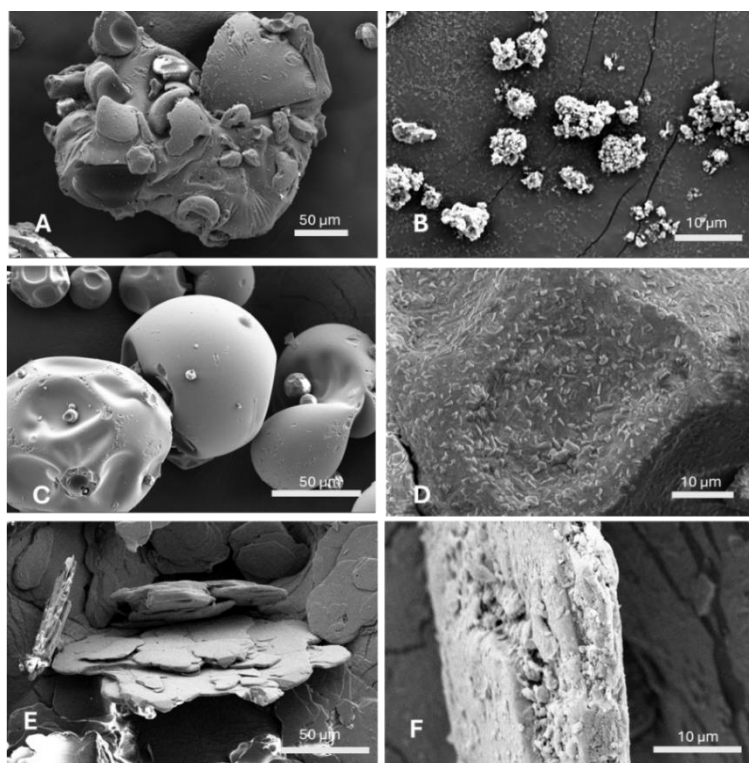


Figure 1- SEM images of cyclodextrins and leucine before and after pKSD processing. A) HPBCD before pKSD; B) FBZ-HPBCD pKSD; C) SBECD before pKSD; D) FBZ-SBECD pKSD; E) Leucine before pKSD; F) FBZ-Leu pKSD.

The pKSD process reduced the particle size of both L-Leucine and HPBCD, due to their distinct particle morphologies (Fig. 1A and E). L-Leucine, with its lamellar structure, exhibited an approximate 3.3-fold decrease in size, as its thin cross-section offers low resistance to crack propagation [8] (Fig. 2C). HPBCD, characterized by an irregular shape, underwent a 17-fold reduction in particle size after pKSD, resulting in finer particles (d_{50} : $1.66 \pm 0.08 \mu\text{m}$). Its irregular morphology likely facilitates the initiation and propagation of cracks (Fig. 1A). Ultimately, HPBCD and leucine's particle morphology influences particle breakage during processing, resulting in a decrease in particle size after the pKSD process. The decrease in particle size directly relates to the improved aerosol performance, with approximately 50% of the emitted dose having an aerodynamic particle size of less than $5 \mu\text{m}$ (Table 1). Leucine-pKSD and HPBCD-pKSD samples demonstrated comparable aerosol performance to commercially approved dry powders for inhalation (Relvar Ellipta, Foster NEXThaler, Symbicort Turbohaler), which typically report PPFs of 20-60% [9].

Table 1. Aerosol performance of FBZ-pKSD samples

Parameters	FBZ-HPBCD	FBZ-SBECD	FBZ-Leu
Emitted dose (ED, μg)	1984.47 ± 11.89	1863.32 ± 38.94	1143.11 ± 41.17
Fine particle dose (FPD, μg)	832.83 ± 103.28	209.9 ± 30.09	548.40 ± 10.12
Fine particle fraction (FPF, %)	48.74 ± 5.11	21.98 ± 1.84	51.58 ± 1.25
Mass Median Aerodynamic Diameter (MMAD, μm)	6.7 ± 0.39	-	5.16 ± 0.08

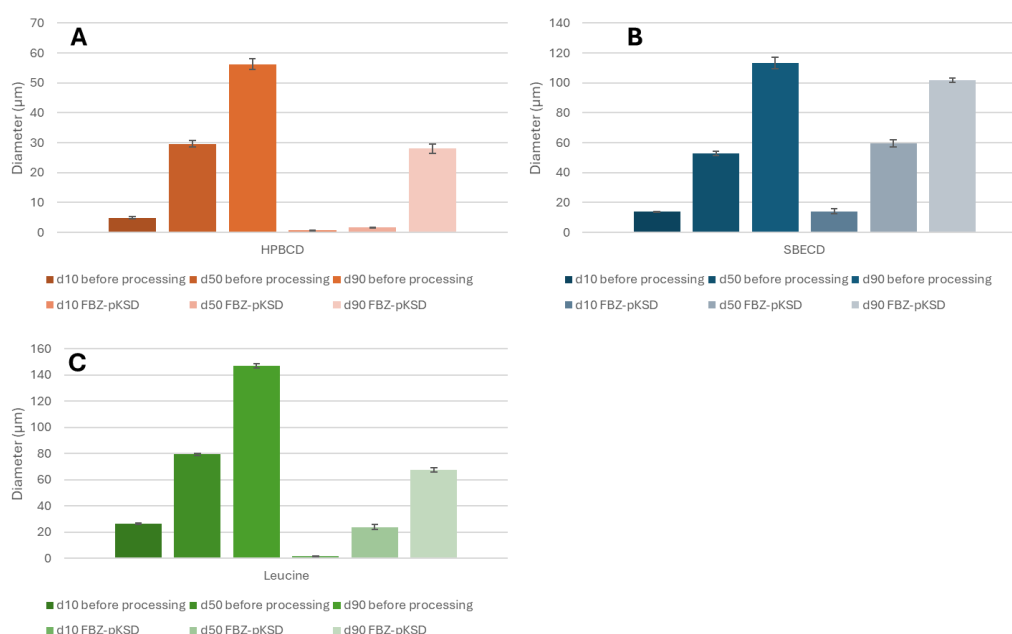


Figure 2- A) Particle size distribution of HPBCD before processing and FBZ-HPBCD pKSD. B) Particle size distribution of SBECD before processing and FBZ-SBECD pKSD. C) Particle size distribution of Leucine before processing and FBZ-Leu pKSD.

The SBECD-pKSD sample was characterized by particles with a spherical and hollow morphology, and they maintained their shape and size after the pKSD process (Fig. 1B and 1C). This observed resistance to particle size change was attributed to the inherent strength associated with spherical particles, as reported by Han et al. [10]. Additionally, the amorphous morphology of SBECD contributes to its lower

plastic stiffness compared to crystalline materials, which further reduces the likelihood of particle breakage during processing [6]. Consequently, the larger particle size of SBECD post-pKSD processing resulted in reduced aerosol performance for FBZ-SBECD (21% FPF) compared to FBZ-HPBCD and FBZ-Leu. However, given that its particle size ($d_{10} > 10 \mu\text{m}$) remains relatively unchanged, SBECD post-pKSD processing presents as an interesting excipient for nasal drug delivery applications as well (Figure 2B)[11].

Table 2. Bulk density before and after pKSD processing

Bulk density (g/mL)	FBZ-HPBCD	FBZ-SBECD	FBZ-Leu
Before pKSD process	0.43 ± 0.01	0.56 ± 0.01	0.35 ± 0.01
After pKSD process	0.38 ± 0.00	0.50 ± 0.00	0.34 ± 0.02

Additionally, the pKSD process had minimal impact on the bulk density of powder blends. The pKSD samples maintained a density similar to or slightly greater than reported for spray-dried powders (e.g., 0.03–0.3g/mL) [12]. A higher powder payload per capsule unit will allow the delivery of a high-dose drug for inhalation. For example, a commercially available spray-dried powder contains 42 mg dose per capsule (Inbrija®) [13]. On the other hand, the pKSD sample FBZ-HPBCD can be loaded in the 60–80 mg range based on its higher bulk density.

Conclusion

The study confirms that the physicochemical characteristics of the excipient (e.g., particle size, morphology, bulk density, and solid state) influenced the particle breakage of the pKSD powder aggregates, which consequently affected the aerosol performance of the resulting powders. HPBCD and leucine powder blends exhibited reduced particle size and improved aerosol performance after the pKSD process. On the other hand, the SBECD-pKSD sample maintained its morphology and particle size and exhibited lower FPF. Additionally, the bulk density for pKSD powders allows for greater capsule loadings compared to spray-dried powders. These findings demonstrate the use of pKSD in engineering particles as a rapid and solvent-free technology to prepare powders for pulmonary delivery. Further research will consider factors such as the influence of particle hardness on breakage mechanisms, morphological changes, and size reduction processes, which can also provide insight into the design space for the manufacturing of high-dose drug powders for inhalation using pKSD processing.

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References

- [1] A. Jüptner and R. Scherließ, "Spray Dried Formulations for Inhalation—Meaningful Characterisation of Powder Properties," *Pharmaceutics*, vol. 12, no. 1, Art. no. 1, Jan. 2020, doi: 10.3390/pharmaceutics12010014.
- [2] D. J. Ellenberger, D. A. Miller, and R. O. Williams, "Expanding the Application and Formulation Space of Amorphous Solid Dispersions with KinetiSol®: a Review," *AAPS PharmSciTech*, vol. 19, no. 5, pp. 1933–1956, July 2018, doi: 10.1208/s12249-018-1007-2.
- [3] D. K. Tan, D. A. Davis, D. A. Miller, R. O. Williams, and A. Nokhodchi, "Innovations in Thermal Processing: Hot-Melt Extrusion and KinetiSol® Dispersing," *AAPS PharmSciTech*, vol. 21, no. 8, p. 312, Nov. 2020, doi: 10.1208/s12249-020-01854-2.
- [4] S. V. Jermain *et al.*, "Homogeneity of amorphous solid dispersions – an example with KinetiSol®," *Drug Dev. Ind. Pharm.*, vol. 45, no. 5, pp. 724–735, May 2019, doi: 10.1080/03639045.2019.1569037.
- [5] M. O. Jara *et al.*, "Comparative study of Hot-Melt Extrusion, spray drying, and KinetiSol® processing to formulate a poorly water-soluble and thermolabile drug," *Int. J. Pharm.*, vol. 676, p. 125582, May 2025, doi: 10.1016/j.ijpharm.2025.125582.
- [6] S. Pazesh, A.-S. Persson, J. Berggren, and G. Alderborn, "Effect of milling on the plastic and the elastic stiffness of lactose particles," *Eur. J. Pharm. Sci.*, vol. 114, pp. 138–145, Mar. 2018, doi: 10.1016/j.ejps.2017.12.001.
- [7] (616) *Bulk Density and Tapped Density of Powders*. doi: 10.31003/uspnf_m99375_02_01.
- [8] A. Norazirah, S. H. S. Fuad, and M. H. M. Hazizan, "The Effect of Size and Shape on Breakage Characteristic of Mineral," *Procedia Chem.*, vol. 19, pp. 702–708, Jan. 2016, doi: 10.1016/j.proche.2016.03.073.
- [9] H. Watz *et al.*, "Targeting the Small Airways with Inhaled Corticosteroid/Long-Acting Beta Agonist Dry Powder Inhalers: A Functional Respiratory Imaging Study," *J. Aerosol Med. Pulm. Drug Deliv.*, vol. 34, no. 5, pp. 280–292, Sept. 2021, doi: 10.1089/jamp.2020.1618.
- [10] J. Han, J. Fitzpatrick, K. Cronin, and S. Miao, "Investigation of the influence of powder characteristics on the breakage of dairy powders," *Food Res. Int.*, vol. 150, p. 110775, Dec. 2021, doi: 10.1016/j.foodres.2021.110775.
- [11] Z. Warnken, Y. J. Kim, H. M. Mansour, R. O. Williams, and H. D. C. Smyth, "Fundamentals in nasal drug delivery," in *Inhalation Aerosols*, 3rd ed., CRC Press, 2019.
- [12] C. Bosquillon, C. Lombry, V. Pr  at, and R. Vanbever, "Influence of formulation excipients and physical characteristics of inhalation dry powders on their aerosolization performance," *J. Controlled Release*, vol. 70, no. 3, pp. 329–339, Feb. 2001, doi: 10.1016/S0168-3659(00)00362-X.
- [13] I. Sibum, P. Hagedoorn, A. H. de Boer, H. W. Frijlink, and F. Grasmeijer, "Challenges for pulmonary delivery of high powder doses," *Int. J. Pharm.*, vol. 548, no. 1, pp. 325–336, Sept. 2018, doi: 10.1016/j.ijpharm.2018.07.008.