Research Article

Fabrication of Agglomerated Lactose Using Fluidized Bed for Good Compressibility

Bo Wang,¹ Huijie Li,¹ Jia Xiang,¹ Jiao Zheng¹ ² and Junyan Wang³

¹Xiangya School of Pharmaceutical Sciences, Central South University, Changsha, Hunan 410000, China

²Drug Clinical Trial Institution Department, Hunan Provincial People's Hospital (The First Affiliated Hospital of Hunan Normal University), Changsha, Hunan 410000, China

³Faculty of Engineering, Monash University, Melbourne 3800, Australia

Correspondence should be addressed to Jiao Zheng; zhengjiao51@163.com and Junyan Wang; junyan.wang@monash.edu

Received 6 March 2021; Revised 12 March 2021; Accepted 10 April 2021; Published 6 May 2021

Academic Editor: Tingting Hong

Copyright © 2021 Bo Wang et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

In this work, a fluidized bed agglomeration process was used to produce agglomerated lactose with good compressibility. In the fluidized bed agglomeration, large lactose crystals were used as the core materials, fine-milled lactose particles were bound to the surface of large lactose cores, and lactose solution was used as the binder. A suspension of lactose solution is sprayed onto the fluidized lactose particles, forming liquid bridges among the large and small lactose particles to form agglomerated lactose. Good hardness of 75–88 N was achieved for the agglomerated lactose. The particle size and bulk density can be controlled. The effects of agglomeration parameters, including solution concentration and temperature, atomizing pressure, peristalsis speed, and material temperature, were investigated for the agglomeration result and the characteristics of the agglomerated lactose. The result also shows that high solution temperature and high solution concentration can improve fluidized bed agglomeration efficiency.

1. Introduction

Excipients are inactive substances formulated with the active pharmaceutical ingredient (API) of a medication. Many excipients, like lactose, starch, and microcrystalline cellulose, contribute to the property, stability, safety, and many other aspects of drug manufacturing and have been widely used in the pharmaceutical industry [1]. Different kinds of excipients are frequently used together to achieve multiple properties for a medication; meanwhile, the ones that can improve the quality of pharmaceutical preparations or the production efficiency have attracted more and more attention [1, 2]. For instance, there have been several types of lactose excipient [3, 4], which have typical values of fluidity, viscosity, compressibility, particle size and particle size distribution, enteric disintegration performance, and so on. These values have great influence on the physical and chemical properties of pharmaceutical preparations, such as disintegration and dissolution and bioequivalence *in vivo* and *in vitro*. In practice, solid dosage forms require different types of excipients to be added to

the API in order to obtain the desired physicochemical properties, such as flowability, compressibility, disintegration, solubility, and stability [4–8], for the medication. The excipients are mixed and granulated with the APIs using different equipment to ensure their mixing uniformity. The typical mixing and granulation techniques in the pharmaceutical industry include direct mixing, dry and wet granulation, spray drying, and freeze drying [9].

Agglomeration is the technique that binds small particles to create large aggregates. It is also presented as granulation in a macro sense, where pharmaceutical ingredients are frequently granulated with some excipients to create visible round particles for production of tablets and capsules [5, 6]. Through agglomeration/granulation technology, the APIs and excipients can be evenly mixed with a suitable particle size distribution and provide good material uniformity, fluidity, and compressibility for the subsequent preparation process, such as the tableting process [7]. A good agglomeration/granulation also contributes to the stability in transportation and storage, provides desired disintegration and

dissolution, and ensures that the drug has the expected dissolution curve and AUC (area under the curve) *in vivo*, ensuring good absorption of the drug for a better therapeutic effect.

At present, typical agglomeration/granulation includes the formation of solid bridges, adhesion, sintering, chemical reaction, crystallization, and colloidal particle deposition [8, 9], among which dry granulation and wet granulation are the two main methods in practice [2, 10]. The dry granulation methods generally bind the fine particles by compression force, for those materials with good compressibility, namely, high molecular interactions. The wet granulation methods use a solvent (i.e., water), solution, or suspension as the binder to provide bridging forces required for the fine powders to form large particles. In this work, a fluidized bed agglomeration process was used to produce the agglomerated lactose. A suspension of lactose solution is sprayed onto the fluidized lactose particles, forming liquid bridges among the large and small lactose particles to form agglomerated lactose. The effects of agglomeration parameters, including solution concentration and temperature, atomizing pressure, peristalsis speed, and material temperature, were investigated for the agglomeration.

2. Materials and Methods

2.1. Preparation of Lactose Suspension. The pharmaceutical-grade α -lactose monohydrate (>99.9%) was purchased from Jiangsu Dawning Pharmaceutical Co., Ltd., China. Four groups of lactose solution were prepared with lactose concentrations of 5%, 15%, 25%, and 40% (*w/w*) using the α -lactose monohydrate. The lactose solutions were added with 10% (*w/w*) fine-milled lactose of 300 mesh (Jiangsu Dawning Pharmaceutical) for efficient granulation [11] to obtain lactose suspension samples as the agglomeration binder. Adding lactose into the solution to prepare suspension is to increase wet particles in the fluidized bed, increasing effective collision between particles, accelerating particle adhesion, and increasing agglomeration rate.

2.2. Agglomeration. The schematic diagram of the fluidized bed granulator and the agglomeration parameters is shown in Figure 1. In a typical agglomeration, 120 g milled lactose of 120 mesh and 100 g fine-milled lactose of 300 mesh were mixed and added into a fluidized bed granulator (Shenzhen Xinyite Technology Co., Ltd, China). The fluidized bed granulator was preheated for 30 minutes. 150 mL lactose suspension was gradually sprayed onto the fluidized lactose mixture in the granulator at a controlled spraying speed. 5 min of the subdry process was performed to ensure a stable temperature of the materials in the fluidized bed. An additional volume of 150 mL of lactose suspension was sprayed subsequently in order to investigate the effect of the binder. The agglomeration stopped after 600 mL lactose suspension was sprayed in total. The concentration, temperature, peristaltic speed, and atomizing pressure were investigated for the lactose agglomeration.

2.3. Product Characteristics. The calculation of the D_{50} value is generally used as a representative parameter of the particle

Granulation condition

Parameter	Setting
Spray rate (ml/min)	10
Spray pressure (MPa)	0.2
Inlet temperature (°C)	80
Material temperature (°C)	30~40
Spray/Sub-dry duration (min)	15/5

FIGURE 1: Schematic diagram of the fluidized bed granulator and the agglomeration parameters.

size in a fluidized bed granulation process. The particle size distribution (D_{50} values) was determined by a laser scattering particle size distribution analyzer LA-960 (Horiba, Japan). The agglomeration rate constant (K) is defined as a function of D_{50} , calculated by linear regression, using the following equation:

$$D_{50,t} = K \cdot t + D_{50,t=0}, \quad (1)$$

where $D_{50,t}$ is the average particle size of the particles at time t , $D_{50,t=0}$ is the average particle size of the raw material before agglomeration, and t is the agglomeration time.

The bulk density was determined for the agglomerated lactose samples. The samples were gently and uniformly filled into the cylinder to 50 cm². The weight of the filled powder was measured. The bulk density ρ was determined with $\rho = M/V$ (mass over volume). The tablet hardness was measured to evaluate the compressibility of the agglomerated lactose. Typically, 0.25 g agglomerated lactose was compressed with a diameter of 8 mm on a single-punch tablet press under a compression pressure of 10 MPa. The tablet hardness was measured in a hardness tester (Tianjin Jingtuo, China) three times to obtain the average value.

DSC analysis was performed using a differential scanning calorimeter (HSC-4 DSC, Henven, China) for the agglomerated lactose. The sample for DSC measurement was prepared following standard procedures using a sealed aluminum pan. About 5 mg of sample was used in the analysis. The sample

TABLE 1: The particle characteristics of the agglomerated lactose fabricated with different lactose concentrations and sprayed volume of lactose suspension.

Lactose concentration (w/w)	Sprayed volume (mL)	D_{50} (μm)	K ($\mu\text{m}/\text{min}$)	Bulk density (g/mL)	Tablet hardness (N)
5%	150	60.00	0.62	0.4708	75.21
	300	66.91		0.4948	76.55
	450	78.43		0.5032	78.22
	600	87.56		0.5229	78.76
15%	150	64.11	0.70	0.4823	76.23
	300	69.83		0.5022	77.22
	450	84.22		0.5243	78.43
	600	92.55		0.5492	80.21
25%	150	72.32	1.98	0.4874	78.34
	300	107.59		0.5121	80.54
	450	130.89		0.5317	81.28
	600	169.28		0.5618	83.45
40%	150	79.21	2.16	0.4924	85.21
	300	118.32		0.5282	87.31
	450	140.76		0.5508	87.92
	600	179.44		0.6022	88.34

FIGURE 2: The change in particle size D_{50} as functions of lactose concentration and spraying volume of the lactose suspension.

was heated from room temperature of 25°C to 300°C using a ramp rate of 5°C/min, with N_2 as the purge gas. Heat flow as a function of increasing temperature was recorded for the analysis of each sample. Fourier transform infrared (FTIR) spectroscopy was used to investigate the agglomerated lactose and the raw material (α -lactose monohydrate). The specimen was mixed with KBr powder, tableted, and scanned for transmission sensitivity in a Nicolet 6700 FTIR spectrometer (Thermo Fisher Scientific). The FTIR spectra used a resolution of 1 cm^{-1} with 64 scans. The agglomerated lactose sample manufactured with the 40% lactose suspension was

FIGURE 3: The change in bulk density of agglomerated lactose as functions of lactose concentration and spraying volume of the lactose suspension.

FIGURE 4: The change in tablet hardness as functions of lactose concentration and spraying volume of the lactose suspension.

placed on carbon tape on an aluminum sample spike. The gold-plated particles were observed by a JSM-7200F scanning electron microscope (SEM, JEOL Ltd.). XRD analysis was used to investigate the crystalline characteristics of the agglomerated lactose. Solid samples were loaded on powder holders and analyzed using a Siemens D5000 diffractometer. During the XRD detection, the samples were scanned from 5° to 40° with a scanning rate of 0.02°/s, a scanning current of 30 mA, and a scanning voltage of 40 kV.

3. Results and Discussion

Due to its relatively mild process and stable raw material properties, the loss of material weight for the production is

FIGURE 5: SEM images of the agglomerated lactose manufactured with the 40% lactose suspension showing fine-milled lactose on the particle surface. Scale bars: 10 μm (a), 1 μm (b).

less than 5%. The yield of the agglomeration process is over 95%, where some loss was induced by the air blowing in the fluidized bed equipment. Table 1 shows the measured particle size D_{50} , agglomeration rate constant K , bulk density, and tablet hardness. The result suggests that the particle size of agglomerated lactose largely increases with the lactose concentration (w/w) and the sprayed volume of binder solution (Figure 2), as more lactose has been added to the agglomeration system. High lactose weight concentration (w/w) and the sprayed volume of binder solution also contribute to the viscosity and binding efficiency for a high agglomeration rate constant. The bulk density and tablet hardness increase with the lactose concentration and the sprayed volume, since the ratio of large lactose of 300 mesh (which has relatively lower bulk density and compressibility) decreases.

In the agglomeration process, wet particles form liquid bridges when they coalesce. In the subsequent drying step, the solid bridges that hold the particles together form large particles from the liquid bridges. When the solution has a lactose concentration of 25%, the agglomeration rate constant K is relatively high compared to other binders. As reported by Fujiwara et al. [12], 10% PVP solution has a K value of 2.17, 10% HPMC has a K value of 1.16, and 8% HPC solution has a K value of 1.71. With the lactose solution and suspension as the binder, the bulk density and compressibility of lactose powder increase as functions of the agglomeration

FIGURE 6: DSC spectrum of the agglomerated lactose.

parameters. As shown in Figure 3, when the particle size of lactose increases with the granulation time, its bulk density will gradually increase with the increase of the particles. For the same reason, high lactose concentration also increases the agglomeration rate.

Generally, small particles show poor flowability but good compressibility [13]. The result, however, shows that both

FIGURE 7: XRD spectrum of the agglomerated lactose.

FIGURE 8: FTIR spectra of the agglomerated lactose and lactose monohydrate (raw material).

the tablet hardness and the particle size of the agglomerated lactose increase at the same time (Figure 4) for the following possible reason. At a spray pressure of 20 MPa, atomized droplets were smaller than the size of lactose particles, where the agglomerated lactose particles were loose and were composed of fine-milled lactose linked through solid bridges formed after drying. The aggregation of fine particles was confirmed by SEM (Figure 5). The SEM shows that the surface of particles is porous and the structure is fluffy. When the particle size increases, more fine particles are aggregated resulting in increases in the compressibility (due to the number of fine particles) and the flowability (due to the size of the aggregates). The particles would have good flowability and good compressibility when the size is over $140\ \mu\text{m}$ [14]. Besides, the temperature of the solution, the temperature of the material in the fluidized bed chamber and the spraying speed of lactose suspension play important roles in the agglomeration process, improving the granulation speed and efficiency. High temperatures and low spraying speeds of lactose suspension induce fast drying rates of the fluidized

lactose, affecting the binding and formation of solid bridges among the fine lactose particles.

The DSC curve (Figure 6) shows that the agglomerated lactose is lactose monohydrate, where the dehydration peak is shown at 145°C . β -Lactose peak is shown alongside α -lactose peak, indicating that the process transfers α -lactose to β -lactose [15, 16]. According to the XRD spectrum (Figure 7), α -lactose peaks are observed at 2θ of 12.5° , 19.1° , 19.6° , and 19.9° . β -Lactose peaks are at 2θ of 10.5° and 20.8° , indicating that a small amount of β -lactose was produced [17, 18]. The FTIR spectra confirmed that the materials are lactose monohydrate [19] with a peak of -OH of water at $3600\ \text{cm}^{-1}$ (Figure 8).

4. Conclusions

This work used a fluidized bed agglomeration process to produce the agglomerated lactose with good compressibility. In the fluidized bed agglomeration, large lactose crystals were used as the core materials, fine-milled lactose particles were bound to the surface of large lactose cores, and lactose solution was used as the binder. The fine-milled lactose of 300 mesh contributed to the compressibility of the agglomerated lactose. Good harness of the tablets around 75–88 N was achieved when 0.25 g agglomerated lactose was compressed with a diameter of 8 mm on a single-punch tablet press under a compression pressure of 10 MPa. The particle size and bulk density can be controlled. Instrumental analysis indicated the production of β -lactose.

Data Availability

All data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Acknowledgments

This work was supported by the 131 Talent Engineering Fund (2020-32), Scientific Research Project of Hunan Provincial Department of Education (20C1156), Scientific Research Project of Hunan Provincial Health Commission (202115011227), and Clinical Pharmacy Project of Medical Research Fund of Hunan Medical Association (HMA202001008).

References

- [1] J. B. M. Fernandes, M. T. Celestino, M. I. B. Tavares et al., "The development and characterization of propranolol tablets using tapioca starch as excipient," *Anais da Academia Brasileira de Ciências*, vol. 91, no. 1, article e20180094, 2019.
- [2] N. Garg, P. Pandey, D. Kaushik, and H. Dureja, "Development of novel multifunction directly compressible co-processed excipient by melt granulation technique," *International Journal of Pharmaceutical Investigation*, vol. 5, no. 4, pp. 266–274, 2015.

- [3] S. Lute, R. Dhenge, and A. Salman, "Twin screw granulation: effects of properties of primary powders," *Pharmaceutics*, vol. 10, no. 2, p. 68, 2018.
- [4] S. Tan, A. Ebrahimi, and T. Langrish, "Template-directed flower-like lactose with micro-meso-macroporous structure," *Materials & Design*, vol. 117, pp. 178–184, 2017.
- [5] T. Ito, K. Okada, K. H. Leong et al., "A time-domain nmr study of the state of water in wet granules with different fillers and its contribution to the wet granulation process and to the characteristics of granules," *Chemical and Pharmaceutical Bulletin*, vol. 67, no. 3, pp. 271–276, 2019.
- [6] N. Hirai, T. Takatani-Nakase, and K. Takahashi, "Application of near-infrared spectrometry to evaluate the mechanism of wet granulation using a high-speed mixer with porous calcium silicate and sugar alcohols," *Chemical and Pharmaceutical Bulletin*, vol. 66, no. 11, pp. 1027–1034, 2018.
- [7] S. Shanmugam, "Granulation techniques and technologies: recent progresses," *BioImpacts*, vol. 5, no. 1, pp. 55–63, 2015.
- [8] L. Cai, L. Farber, D. Zhang, F. Li, and J. Farabaugh, "A new methodology for high drug loading wet granulation formulation development," *International Journal of Pharmaceutics*, vol. 441, no. 1–2, pp. 790–800, 2013.
- [9] S. M. Iveson, J. D. Litster, K. Hapgood, and B. J. Ennis, "Nucleation, growth and breakage phenomena in agitated wet granulation processes: a review," *Powder Technology*, vol. 117, no. 1–2, pp. 3–39, 2001.
- [10] O. A. Adeleye, M. N. Femi-Oyewo, and M. A. Odeniyi, "The effect of processing variables on the mechanical and release properties of tramadol matrix tablets incorporating Cissus populnea gum as controlled release excipient," *Polymers in Medicine*, vol. 44, no. 4, pp. 209–220, 2014.
- [11] S. A. L. de Koster, K. Pitt, J. D. Litster, and R. M. Smith, "High-shear granulation: an investigation into the granule consolidation and layering mechanism," *Powder Technology*, vol. 355, pp. 514–525, 2019.
- [12] M. Fujiwara, M. Dohi, T. Otsuka, K. Yamashita, and K. Sako, "Influence of binder droplet dimension on granulation rate during fluidized bed granulation," *Chemical and Pharmaceutical Bulletin*, vol. 61, no. 3, pp. 320–325, 2013.
- [13] Y. Kudo, M. Yasuda, and S. Matsusaka, "Effect of particle size distribution on flowability of granulated lactose," *Advanced Powder Technology*, vol. 31, no. 1, pp. 121–127, 2020.
- [14] Y. Özalp, M. M. Onayo, and N. Jiwa, "Evaluation of lactose-based direct tableting agents' compressibility behavior using a Compaction Simulator," *Turkish Journal of Pharmaceutical Sciences*, vol. 17, no. 4, pp. 367–371, 2020.
- [15] S. Tan, A. Ebrahimi, and T. Langrish, "Preparation of core-shell microspheres of lactose with flower-like morphology and tailored porosity," *Powder Technology*, vol. 325, pp. 309–315, 2018.
- [16] S. Tan, A. Ebrahimi, X. Liu, and T. Langrish, "Hollow flower-like lactose particles as potential drug carriers: effect of particle size and feed concentration," *Powder Technology*, vol. 320, pp. 1–6, 2017.
- [17] A. S. Barham and B. K. Hodnett, "In situ X-ray diffraction study of the crystallization of spray-dried lactose," *Crystal Growth & Design*, vol. 5, no. 5, pp. 1965–1970, 2005.
- [18] S. Tan, T. Jiang, A. Ebrahimi, and T. Langrish, "Effect of spray-drying temperature on the formation of flower-like lactose for griseofulvin loading," *European Journal of Pharmaceutical Sciences*, vol. 111, pp. 534–539, 2018.
- [19] S. Tan, A. Ebrahimi, X. Liu, and T. Langrish, "Role of templating agents in the spray drying and postcrystallization of lactose for the production of highly porous powders," *Drying Technology*, vol. 36, no. 15, pp. 1882–1891, 2018.