Journal Pre-proof

Coating of primary powder particles improves the quality of binder jetting 3D printed oral solid products

Yingya Wang , Natalja Genina , Anette Müllertz , Jukka Rantanen

PII: S0022-3549(22)00362-8
DOI: https://doi.org/10.1016/j.xphs.2022.08.030
Reference: XPHS 2846

To appear in: *Journal of Pharmaceutical Sciences*

Received date: 24 May 2022
Revised date: 11 August 2022
Accepted date: 20 August 2022

Please cite this article as: Yingya Wang , Natalja Genina , Anette Müllertz , Jukka Rantanen , Coating of primary powder particles improves the quality of binder jetting 3D printed oral solid products, *Journal of Pharmaceutical Sciences* (2022), doi: https://doi.org/10.1016/j.xphs.2022.08.030

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 Published by Elsevier Inc. on behalf of American Pharmacists Association.

Coating of primary powder particles improves the quality of binder jetting 3D printed oral solid products

Yingya Wang[ab], Natalja Genina[a], Anette Müllertz[a], and Jukka Rantanen[a]*

[a]*Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark*

[b]*Mille International ApS, Hellerup, Denmark*

*Corresponding author:

Jukka Rantanen

Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen

Universitetsparken 2, 2100 Copenhagen, Denmark

TEL +45 35 33 65 85

E-MAIL jukka.rantanen@sund.ku.dk

Journal Pre-proof

Declarations of interest

Authors including Yingya Wang, Anette Müllertz, and Jukka Rantanen are inventors in the patent application CN113080253A. All authors declare no other conflict of interest.

Abbreviations

3D	Three-dimensional

ACN	Acetonitrile
API	Active Pharmaceutical Ingredient
BJ	Binder Jetting
Ph. Eur.	European Pharmacopoeia
HPLC	High-Performance Liquid Chromatography
PCM	Paracetamol
PVP	Polyvinylpyrrolidone
SEM	Scanning Electron Microscope
XRPD	X-ray Powder Diffraction

Journal Pre-proof

1. Introduction

Binder jetting (BJ) three-dimensional (3D) printing is a powder-based additive manufacturing technology. It constructs the product via a layer-by-layer processing of a given powder bed. For each layer of this powder bed, an ink of binder solution or pure solvent is sprayed onto the surface of powder bed to induce product solidification after jetting. In this work, the material forming the powder bed is referred as primary powder. For fabrication of a pharmaceutical product, the primary powder can comprise a mixture of matrix (i.e., the filler and supporting material), dry binder, active pharmaceutical ingredient (API), and possibly other relevant ingredients. The pattern of each layer can be varied based on the designed overall 3D structure of the final product.

Recently, the application of BJ 3D printing for designing oral solid products has gained an increased interest as BJ shows evident advantages over the traditional pharmaceutical compaction-based processes [1, 2]. The BJ 3D printed product is solidified by particle binding primarily via the formation of solid bridges, which is fundamentally different when compared with the compaction process where brittleness and plastic deformation contribute to the increase in interparticulate interactions [3]. BJ 3D printing can be used to design and print a product with a porous structure, which is especially suitable for fabricating an orodispersible solid dosage form with a short disintegration time (less than 3 minutes) [4]. It also allows for a flexible control of the dose, microstructure, and composition of the solid product [5]. Since BJ is still under development and a relatively new technology in the pharmaceutical field, it is important to understand the underpinning mechanisms related to fabrication of these solid products. Quality target product profile for these orodispersible solid dosage forms has two contradictory elements, namely a fast disintegration and an acceptable mechanical strength of the solid product. One of the current key challenges is a relatively high amount of dry binder needed in the BJ 3D printed product for ensuring sufficient mechanical strength that could in turn negatively affect (prolong) the disintegration time.

It is well-known that development of new excipients is time-consuming and expensive, which justifies exploring methods for improving the performance of existing excipients using traditional pharmaceutical technologies. Fluidized bed coating used for coating of powdered particles without agglomerating them, i.e., the thin layer coating, is an effective method for controlling drug release, taste-masking, and improving flowability and homogeneity of powdered materials [6]. Here, it is hypothesized that pre-processing of the components of primary powder for BJ by fluidized bed coating can improve processability by enhancing the performance of the material and consequently, improve the quality of the final printed product.

This study aims to improve the processability of the primary powder for BJ 3D printing and subsequently the quality of printed oral solid products by pre-processing an existing pharmaceutical excipient, namely lactose powder, via thin layer coating with a coating solution containing polyvinylpyrrolidone (PVP) in the fluidized bed equipment. The coated lactose powder together with

uncoated lactose powder was used as matrix in the primary powder in BJ and compared to the composition only comprising uncoated lactose powder as matrix. PVP was used as the dry binder in the primary powder at three levels. Besides the dry binder and matrix, the primary powder comprised paracetamol (PCM) as a model drug. In this study, we aimed at printing prototypes that can be further developed into an orodispersible solid dosage form.

2. Materials and methods

2.1. Materials

Spherical lactose monohydrate SuperTab® 11SD (referred as lactose powder) was a donation from DFE Pharma (Goch, Germany), and Kollidon® 30 (referred as PVP powder) was purchased from BASF Corporation (Ludwigshafen, Germany). PCM (particle size below 180 µm) was from Fagron A/S (Copenhagen, Denmark). The reagents used in this study were high-performance liquid chromatography (HPLC) grade acetonitrile (ACN) from VWR Chemicals (Radnor, PA, US) and purified water by Ultra Clear™ reverse osmosis system from Evoqua Water Technologies (Barsbüttel, Germany).

2.2. Coating

The exact amount of lactose powder (114 ± 0.5 g) was coated with a 20% w/V PVP aqueous solution by VFC-LAB Micro Flo-Coater from Freud Vector (Marion, IA, US). The air was sprayed from the nozzle at the bottom of the coater at a controlled rate of 165 L/minute, air pressure of 0.1 MPa, inlet air temperature of 50 ℃, and at the pump speed of 3 rpm corresponding to the feeding rate of 0.3 mL/minute of the PVP solution. The coating was done in cycles: 15 minutes coating and 5 minutes fluidizing without the liquid supply for each cycle. The coating process was stopped when the weight gain of 5.2-5.3% (w/w, dry basis) was achieved. The target was to achieve a ratio of lactose:PVP 19:1 after coating, and the obtained powder is referred as coated lactose powder in the following context. After spraying of the coating solution, the powder was fluidized for additional 30 minutes before collecting.

2.3. Preparation of primary powder

Six compositions of primary powder were studied (Table 1). Three compositions contained uncoated lactose powder, and the remaining three compositions had the coated lactose powder in addition to the uncoated powder. In this work, the six compositions followed the coding rule indicated by PVP percentage and uncoated or coated, namely, P10UC, P10C, P15UC, P15C, P20UC and P20C. For example, P10UC means PVP 10% w/w was in the primary powder and only uncoated lactose powder was used. The PCM content was fixed at 30% w/w in all six compositions. In the compositions with uncoated lactose powder, besides API, the primary powder contained dry PVP at three levels of 10%, 15%, and 20% w/w, and the rest of the composition was uncoated lactose powder. In the

compositions with coated lactose powder, besides API, 40% w/w of the primary powder was coated lactose powder, and the rest was dry PVP and uncoated lactose powder to end up with the total PVP content (8%, 13%, or 18% w/w dry PVP plus 2% w/w PVP in the coated lactose powder) to be still at three levels of 10%, 15%, and 20% w/w. All materials were mixed in a Turbula® shaker-mixer (Willy A. Bachofen AG, Muttenz, Switzerland) at 35 rpm for 5 minutes.

2.4. Binder jetting 3D printing

A primary powder was loaded in a BJ 3D printer Easy3DP-M300 (EasyMade, Wuhan, China) equipped with Gen5 piezoelectric printhead (Ricoh China, Shanghai, China). An array of 6 by 6 tablet-shaped products (36 objects in total) was designed by TinkerCAD (Autodesk, Inc., San Rafael, CA, US) to be printed with a diameter of 12 mm and a height of 4.5 mm for each product. The designed objects were exported as a stereolithography file in STL format. The file was uploaded into pattern slicing and process controlling printer software Easy3DColor (EasyMade, Wuhan, China). Each product was constructed with 30 layers of the primary powder at the room temperature, and around 100 µL ink was sprayed per layer. The ink used in this study was 5% w/V PVP aqueous solution. The printed products were kept in the printer with residual primary powder for 10 minutes and transferred to an oven for a 24-hour drying at 50 ℃. After drying, the final products were obtained by manually brushing off the residual primary powder.

2.5. Particle size distribution

Malvern Mastersizer 2000 laser diffractometer (Malvern Panalytical, Malvern, UK) was used to measure the particle size distribution of the uncoated and coated lactose powders. 3-4 g of powder was placed in Scirocco dry sampling system (Malvern Panalytical, Malvern, UK) and dispersed at air pressure of 3 bar and the vibration feeding rate of 50%. The obscuration was in between 0.5% to 6%. Each sample was measured in triplicate. The 10%, 50%, and 90% volume sizes of measured powder were recorded as D10/D50/D90 (µm), and the span was calculated by Equation (1).

$$\text{Span} = \frac{\text{D90} - \text{D10}}{\text{D50}} \quad (1)$$

2.6. Characterizations of printed products

2.6.1. Resistance to crushing

The diametral resistance to crushing of the printed products was measured by Dr. Schleuniger Pharmatron tablet tester 8M (SOTAX AG, Aesch, Switzerland), and each composition was measured six times.

Journal Pre-proof

2.6.2. Disintegration time

Six pieces of printed product from each composition were placed in a tube on the basket-rack and measured by the disintegration time according to European Pharmacopoeia (Ph. Eur.) [7].

2.6.3. Drug content

About 20 mg of printed product from each composition was sampled, weighed precisely, and subsequently dissolved in 50 mL water for HPLC analysis. PCM was separated by a reverse phase C18 column (Kinetex® 00D-4462-AN, Phenomenex, Torrance, CA, US) installed in Agilent 1260 Infinity instrument (Agilent Technologies, Santa Clara, CA, US) with an isocratic method (mobile phase of water-ACN 80:20, V/V, flow rate of 0.15 mL/minute, and injection volume of 5 µL) at the room temperature. At the retention time of 2.1-2.2 minute, PCM peak under the wavelength of 254 nm was detected by 1290 Diode Array detector (Agilent Technologies, Santa Clara, CA, US). The area under curve of PCM peak was recorded, and the sample concentration was calculated by the standard curve of PCM solutions ranging from 0.05 mg/mL to 0.20 mg/mL with a R^2 of 0.9997 (limit of detection 0.004 mg/mL, limit of quantification 0.012 mg/mL), which covered the detected concentrations of all samples. The drug content was indicated by the percentage of detected amount of PCM in the printed product proportional to the theoretical amount of PCM, which is supposed to be 30% w/w of the printed product. The drug content measurement was performed in triplicate for each composition.

2.7. Scanning Electron Microscopy

The surface of PVP powder, uncoated and coated lactose powders, and the cross-section of printed products from six compositions were imaged with TM3030 (Hitachi, Tokyo, Japan) scanning electron microscope (SEM) at 5 kV. Samples were mounted on a carbon tape and coated by a Cressington 108 Auto sputter coater (Ted Pella, Redding, CA, US) with gold for 15 second under argon purging before they were loaded in the SEM.

2.8. X-ray Powder Diffraction

X-ray powder diffraction (XRPD) of PVP powder, uncoated and coated lactose powders, physical mixture of uncoated lactose and PVP powders, and six compositions of the primary powder as well as their printed products were examined by 3040/60 X'Pert PANalytical Pro X-ray diffractometer (PANalytical, Almelo, Netherlands). Samples were placed on the aluminium plate and measured by CuK_{α} radiation at angle (2θ) from 5 to 35° at a rate of 0.067°/sec. The wavelength of radiation was 1.54187 Å at an acceleration voltage of 45 kV and a current of 40 mA.

Journal Pre-proof

2.9. Statistics

The numeric values from all the tests are presented with mean value ± standard deviation. Unpaired t-test was performed with standard routine in Prism 9 (GraphPad Software, San Diego, CA, US) to compare uncoated and coated lactose powders, as well as to compare the printed products at the same level of PVP content but different in composition. The significance is indicated with * $p< 0.05$, ** $p< 0.01$, and *** $p< 0.001$.

3. Results and discussions

3.1. Characteristics of the coated lactose powder

Spherical agglomerated lactose used in this study was manufactured by spray drying, followed by milling and/or sieving to improve the powder compactability and flowability [8, 9]. The particle size of the original uncoated lactose powder was compared to the coated lactose powder, and the results indicated that the coated particles were significantly larger than the uncoated particles (Table 2). According to the D50 values, the size increase of the coated lactose particles was approximately 10 µm in diameter, whereas the theoretical increase due to PVP layering was calculated to be around 1 µm in diameter based on an approximate 5% w/w weight gain. The unexpected change in the particle size can be related to different phenomena besides thin layer coating that occurred simultaneously during coating process. This can be due to particle attrition and elutriation during fluidization [10, 11], consequently causing the loss of small particles that were remained in the air filter of cyclone and could not be collected. It could also be caused by small lactose particles layering onto the surface of bigger lactose particles and being coated/bound together with big particles. These explanations are supported by the observation that particle size distribution became narrower (span became smaller) after coating (Table 2). It is worth mentioning that no agglomeration of powdered particles was visually observed, suggesting that a thin PVP layer dried on the surface of lactose powder before it could cause the permanent binding of lactose particles together.

Based on the SEM images (Figure 1), the surface of uncoated lactose particles possessed a macroscopically rough surface with some typical tomahawk-shaped lactose monohydrate crystals. The surface of lactose particles became smoother after coating, underlying that a thin layer coating of individual lactose particles with PVP was successful. The coating of crystalline lactose with amorphous PVP layer was also confirmed by XRPD results, where the XRPD diffractogram of the coated lactose powder shows the broader Bragg's peaks with lower intensity as compared to the peaks in the XRPD diffractograms of uncoated lactose powder and physical mixture of uncoated lactose and PVP powders (Figure 2). From these results, it can be concluded that PVP coating of lactose powder changed the size, surface morphology, and surface crystallinity of lactose particles.

3.2. Characteristics of binder jetting printed products

Six compositions of the primary powder were successfully printed, and all samples had an acceptable visual appearance (Figure 3). In terms of the weight of the product, all samples were within a range between 270 and 320 mg, and there was no significant difference between the two compositions with or without coated lactose powder at the same level of PVP content (Figure 4A). The 30% w/w theoretical drug loading of PCM in each printed tablet equals to approximately maximum 100 mg API in each printed product, which is lower than a typical therapeutic dose for PCM [12]. It should be noted that in this study, PCM was used as the model API.

The morphology of the cross-section of the printed products was captured with SEM (Figure 5A-5F). Visible macroscopic pores with the longest dimension larger than 200 µm were observed, indicating areas without solid bridges. There were less macroscopic pores in the printed products from compositions containing the coated lactose powder. The original PVP particles as a dry binder used in this study were manufactured by spray drying [13], and they were hollow particles (Figure S1). In the applied fluidized bed coating method, PVP was dissolved in water and sprayed onto lactose particles forming a thin polymer layer on the surface of lactose particles. This pre-process contributed to a better distribution of PVP in the primary powder and a denser microstructure of printed products from compositions containing coated lactose powder with more contact points between particles, which led to the formation of stronger solid bridges (Figure 6). This difference in interparticulate interactions between compositions also affected the mechanical properties of the printed products. The resistance to crushing of P10C and P15C products was significantly higher than that of P10UC and P15UC products, respectively (Figure 4B).

The printed products from all six compositions met the requirement for disintegration for an orodispersible solid dosage form according to Ph. Eur., which should be within 3 minutes (Figure 4C). Counterintuitively, the printed products of P15C and P20C disintegrated faster than P15UC and P20UC, respectively. The disintegration time of P10UC and P10C was generally too fast to be differentiated by the current method. This improvement in disintegration can be a result of a coherent hydrophilic percolating network formed by PVP coating of the primary powder, which is beneficial for water wicking and penetration, as well as the product disintegration in the disintegration medium [14, 15]. In general, the disintegration of a solid product is governed by several mechanisms, which includes often, firstly, the rate-limiting step of wicking and liquid penetration, followed by processes of swelling, strain recovery and dissolution [16]. It is well-known that lactose monohydrate is hydrophilic, but it dissolves relatively slowly in contact with water. In this study, the PVP coating facilitated wicking and liquid penetration into the bound lactose network in the printed products allowing for a faster disintegration.

However, no difference in resistance to crushing was observed between P20UC and P20C. The force needed to crush both P20UC and P20C printed products was more than the double of the level of 40 N, which is the minimum threshold of sufficient crushing force for an orodispersible solid dosage form [17]. This can be due to the presence of a high amount of water-soluble PVP in the primary powder of

P20UC and P20C, which can provide plenty of contact points with lactose particles for the PVP solid bridges formation in the BJ 3D printing process. Therefore, it can be concluded that with a composition containing a high amount of PVP in BJ primary powder, the method of distributing PVP has only a little influence on the binding strength.

To sum up, the printed products from compositions of P10C and P15C had a significant increase in resistance to crushing compared to P10UC and P15UC, respectively. Especially with P10C, its resistance to crushing was increased close to that of P15UC, whereas its disintegration time remained the same as P10UC. The printed products with compositions P15C and P20C significantly decreased the disintegration time compared to P15UC and P20UC, respectively. This means that by pre-processing of lactose particles via coating with PVP, the amount of PVP used in the BJ 3D printed solid products can be reduced, for instance from 15% to 10% w/w, while still maintaining the comparable characteristics of the BJ 3D printed products. The obtained printed products showed suitable properties for an orodispersible solid dosage form, while some aspects still need further research and optimization, such as addition of a taste-masking agent to mask the potentially unpleasant taste of the API. Furthermore, friability of printed solid objects can be investigated, as it can be an issue for BJ 3D printed products [18-20].

Drug content of the printed products from six compositions is presented in Figure S2. There was no significant difference between the two compositions with or without coated powder at the same level of PVP content. Drug content of P15UC, P15C, P20UC and P20C were slightly lower than 100%, which can be resulted from particle segregation during printing process [21]. The XRPD analysis of printed products (Figure S3) shows that the crystallinity of the products decreased after printing when compared to the primary powder, as amorphous PVP formed solid bridges between crystalline lactose particles, and therefore, the surface crystallinity of the primary powder was partially masked.

4. Conclusion

Pre-processing by thin layer coating of the matrix material in the primary powder for BJ 3D printing successfully changed the interparticulate interactions. This led to more contact points and strengthened the solid bridges formed between particles in the printed products. The coating approach significantly improved resistance to crushing of the printed products and simultaneously decreased the disintegration time of the products, especially with samples having a relatively low amount (10% and 15% w/w) of the binder in the composition. The fabricated solid products by this BJ method met the Ph. Eur. criterium for fast disintegration as an orodispersible solid dosage form.

5. Acknowledgements

Authors would like to thank the financial support from Mille International ApS for the PhD project of Y.W., and the donation of materials from DFE Pharma.

6. Funding

Journal Pre-proof

This research work was financially supported by Mille International ApS.

7. References

1. Sen K, Mehta T, Sansare S, Sharifi L, Ma AWK, Chaudhuri B. Pharmaceutical applications of powder-based binder jet 3D printing process – A review. Adv Drug Deliv Rev. 2021:113943. doi: 10.1016/j.addr.2021.113943.
2. Jamroz W, Szafraniec J, Kurek M, Jachowicz R. 3D Printing in Pharmaceutical and Medical Applications-Recent Achievements and Challenges. Pharm Res. 2018;35(9):176. doi: 10.1007/s11095-018-2454-x.
3. Vromans H, De Boer AH, Bolhuis GK, Lerk CF, Kussendrager KD, Bosch H. Studies on tableting properties of lactose. Part 2. Consolidation and compaction of different types of crystalline lactose. Pharm Weekbl Sci. 1985;7(5):186-93. doi: 10.1007/BF02307575.
4. European Pharmacopoeia. Tablets (01/2018:0478). 10th Edition. Strasbourg (FR): Council Of Europe: European Directorate for the Quality of Medicines and Healthcare; 2019. p. 939.
5. Rahman Z, Charoo NA, Kuttolamadom M, Asadi A, Khan MA. Printing of personalized medication using binder jetting 3D printer. In: Faintuch J, Faintuch S, editors. Precision Medicine for Investigators, Practitioners and Providers. 1 ed. London: Academic Press; 2020. p. 473-81.
6. Hemati A, Cherif R, Saleh K, Pont V. Fluidized bed coating and granulation: influence of process-related variables and physicochemical properties on the growth kinetics. Powder Technol. 2003;130(1-3):18-34. doi: 10.1016/S0032-5910(02)00221-8.
7. European Pharmacopoeia. 2.9.1 Disintegration of tablets and capsules (01/2020:20901). 10th Edition. Strasbourg (FR): Council Of Europe: European Directorate for the Quality of Medicines and Healthcare; 2019. p. 323.
8. DFE Pharma: SuperTab® 11SD Production Information. https://dfepharma.com/Excipients/Expertise/Oral-Solid-Dose/Lactose/Spray-dried/SuperTab-11SD Accessed May 18 2022.
9. Lamesic D, Planinsek O, Lavric Z, Ilic I. Spherical agglomerates of lactose with enhanced mechanical properties. Int J Pharm. 2017;516(1-2):247-57. doi: 10.1016/j.ijpharm.2016.11.040.
10. Cruz N, Briens C, Berruti F. Green sand reclamation using a fluidized bed with an attrition nozzle. Resour Conserv Recy. 2009;54(1):45-52. doi: 10.1016/j.resconrec.2009.06.006.
11. Ma X, Kato K. Effect of interparticle adhesion forces on elutriation of fine powders from a fluidized bed of a binary particle mixture. Powder Technol. 1998;95(2):93-101. doi: Doi 10.1016/S0032-5910(97)03262-2.
12. Hyllested M, Jones S, Pedersen J, Kehlet H. Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: a qualitative review. Br J Anaesth. 2002;88(2):199-214. doi: 10.1093/bja/88.2.199.
13. BASF: Technical Information Kollidon®25, Kollidon®30, Kollidon®30 LP, Kollidon® 90 F. https://pharma.basf.com/technicalinformation/30034974/kollidon-30 Accessed May 18 2022.
14. Quodbach J, Kleinebudde P. A critical review on tablet disintegration. Pharm Dev Technol. 2016;21(6):763-74. doi: 10.3109/10837450.2015.1045618.
15. Shotton E, Leonard GS. The effect of intra- and extragranular maize starch on the disintegration of compressed tablets. J Pharm Pharmacol. 1972;24(10):798-803. doi: 10.1111/j.2042-7158.1972.tb08886.x.
16. Markl D, Zeitler JA. A Review of Disintegration Mechanisms and Measurement Techniques. Pharm Res. 2017;34(5):890-917. doi: 10.1007/s11095-017-2129-z.
17. Schiermeier S, Schmidt PC. Fast dispersible ibuprofen tablets. Eur J Pharm Sci. 2002;15(3):295-305. doi: 10.1016/s0928-0987(02)00011-8.

18. Antic A, Zhang J, Amini N, Morton D, Hapgood K. Screening pharmaceutical excipient powders for use in commercial 3D binder jetting printers. Adv Powder Technol. 2021;32(7):2469-83. doi: 10.1016/j.apt.2021.05.014.
19. Tian P, Yang F, Yu LP, Lin MM, Lin W, Lin QF, et al. Applications of excipients in the field of 3D printed pharmaceuticals. Drug Dev Ind Pharm. 2019;45(6):905-13. doi: 10.1080/03639045.2019.1576723.
20. Yu DG, Shen XX, Branford-White C, Zhu LM, White K, Yang XL. Novel oral fast-disintegrating drug delivery devices with predefined inner structure fabricated by three-dimensional printing. J Pharm Pharmacol. 2009;61(3):323-9. doi: 10.1211/jpp.61.03.0006.
21. Infanger S, Haemmerli A, Iliev S, Baier A, Stoyanov E, Quodbach J. Powder bed 3D-printing of highly loaded drug delivery devices with hydroxypropyl cellulose as solid binder. Int J Pharm. 2019;555:198-206. doi: 10.1016/j.ijpharm.2018.11.048.

Journal Pre-proof

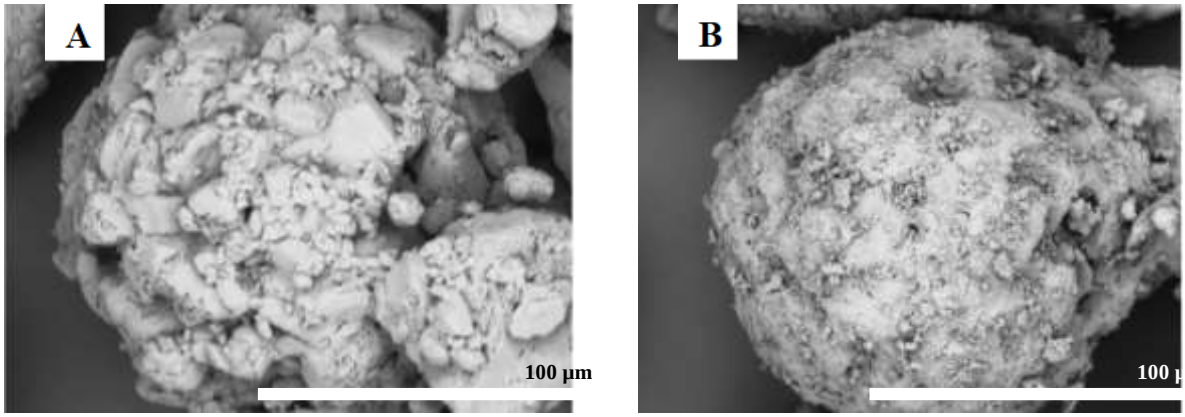

Figure 1 Representative scanning electron microscope images of (A) original uncoated lactose particle and (B) coated lactose particle with polyvinylpyrrolidone.

Journal Pre-proof

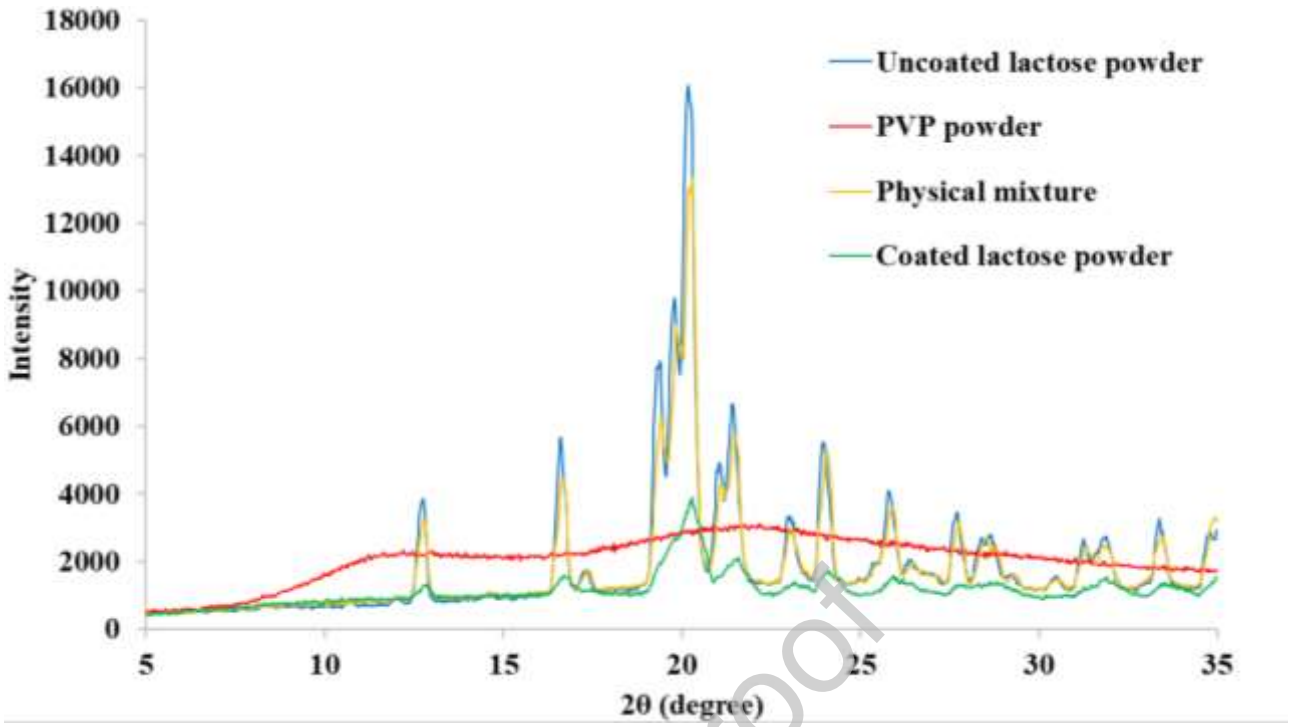

Figure 2 X-ray powder diffraction patterns of uncoated lactose powder (blue line), polyvinylpyrrolidone (PVP) powder (red line), physical mixture of uncoated lactose and PVP powders (yellow line), and coated lactose powder with PVP (green line).

Journal Pre-proof

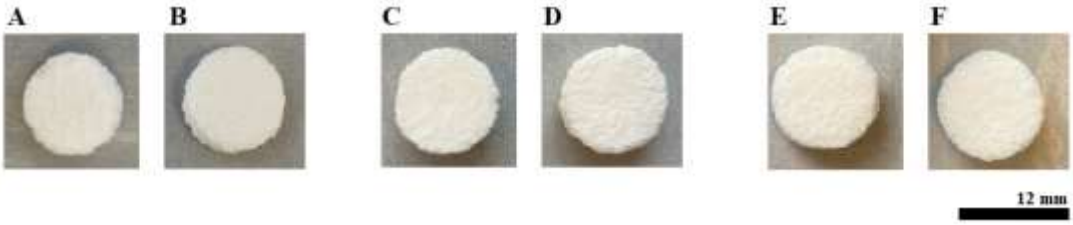

Figure 3 Photographs of printed products from primary powders of (A) 10% w/w polyvinylpyrrolidone (PVP) in composition containing uncoated lactose (P10UC), (B)10% w/w PVP in composition containing coated lactose and uncoated lactose (P10C), (C) 15% w/w PVP in composition containing uncoated lactose (P15UC), (D) 15% w/w PVP in composition containing coated lactose and uncoated lactose (P15C), (E) 20% w/w PVP in composition containing uncoated lactose (P20UC), and (F) 20% w/w PVP in composition containing coated lactose and uncoated lactose (P20C).

Journal Pre-proof

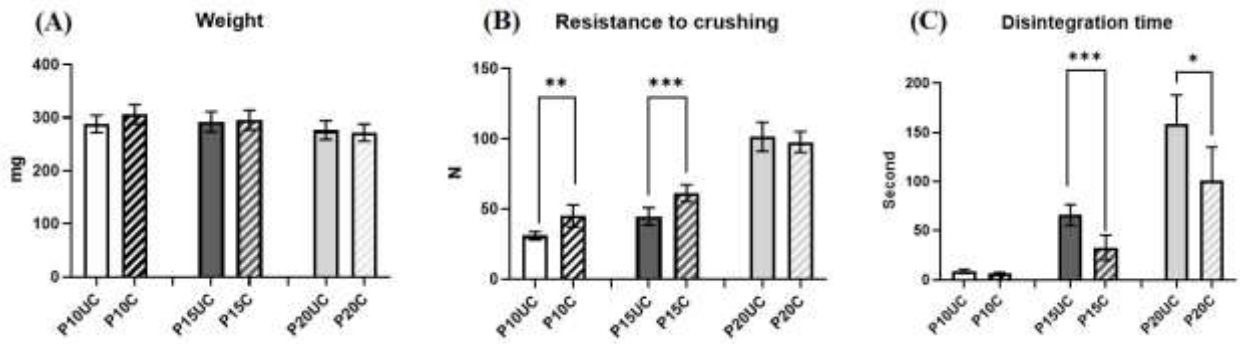

*Figure 4 (A) weight, (B) resistance to crushing, and (C) disintegration time of printed products 10% w/w polyvinylpyrrolidone (PVP) in composition containing uncoated lactose (P10UC), 10% w/w PVP in composition containing coated lactose and uncoated lactose (P10C), 15% w/w PVP in composition containing uncoated lactose (P15UC), 15% w/w PVP in composition containing coated lactose and uncoated lactose (P15C), 20% w/w PVP in composition containing uncoated lactose (P20UC), and 20% w/w PVP in composition containing coated lactose and uncoated lactose (P20C). Values are presented in mean ± standard deviation, n=6. The statistic comparison is performed between the two compositions at the same level of PVP content, and the significance is indicated with * p< 0.05, ** p< 0.01, *** p< 0.001.*

Journal Pre-proof

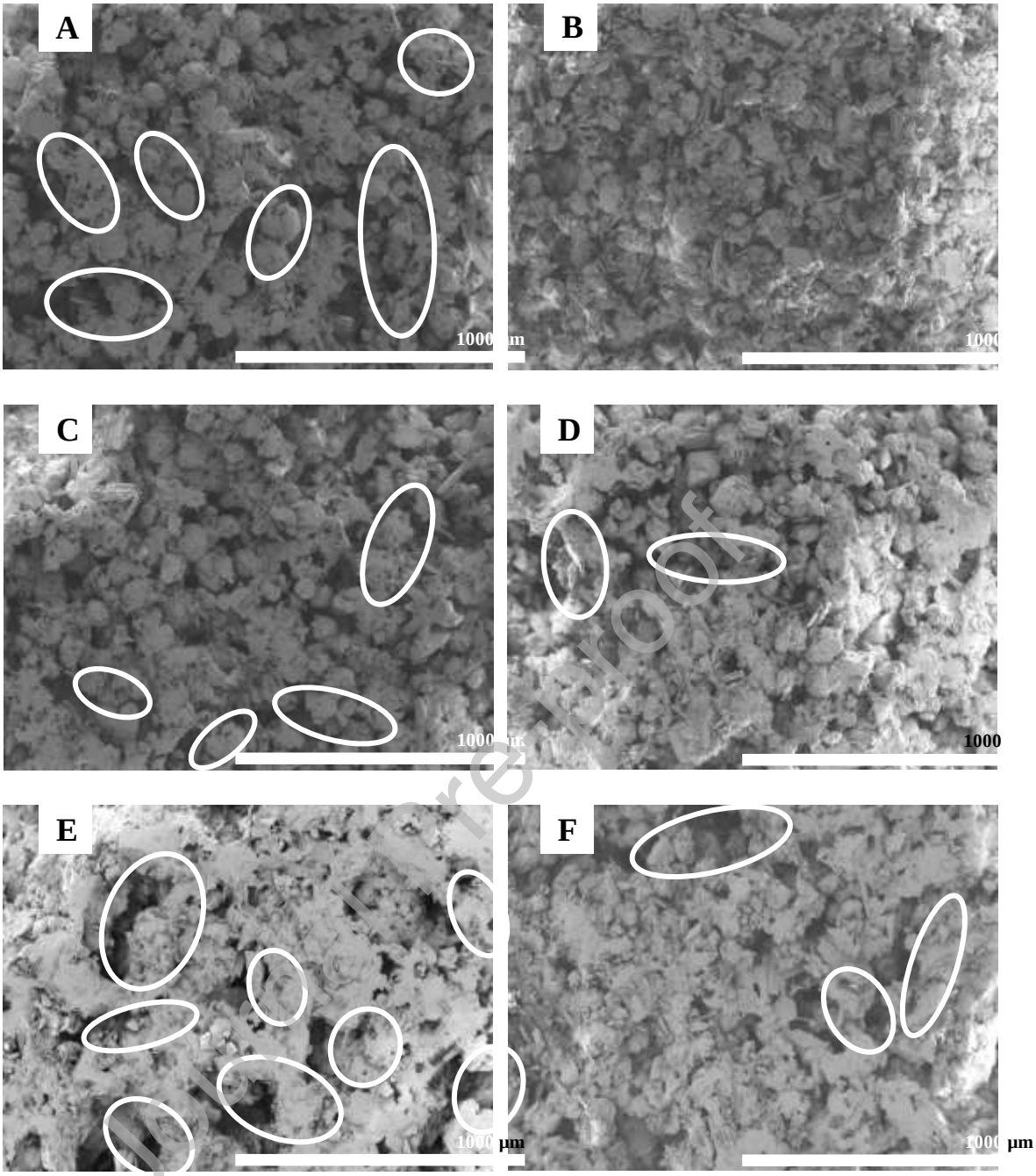

Figure 5 Representative scanning electron microscope images of cross-section of printed products from primary powders of (A) 10% w/w polyvinylpyrrolidone (PVP) in composition containing uncoated lactose (P10UC), (B)10% w/w PVP in composition containing coated lactose and uncoated lactose (P10C), (C) 15% w/w PVP in composition containing uncoated lactose (P15UC), (D) 15% w/w PVP in composition containing coated lactose and uncoated lactose (P15C), (E) 20% w/w PVP in composition containing uncoated lactose (P20UC), and (F) 20% w/w PVP in composition containing coated lactose and uncoated lactose (P20C). Visible macroscopic pores with the longest dimension larger than 200 µm in printed products are marked with white circle.

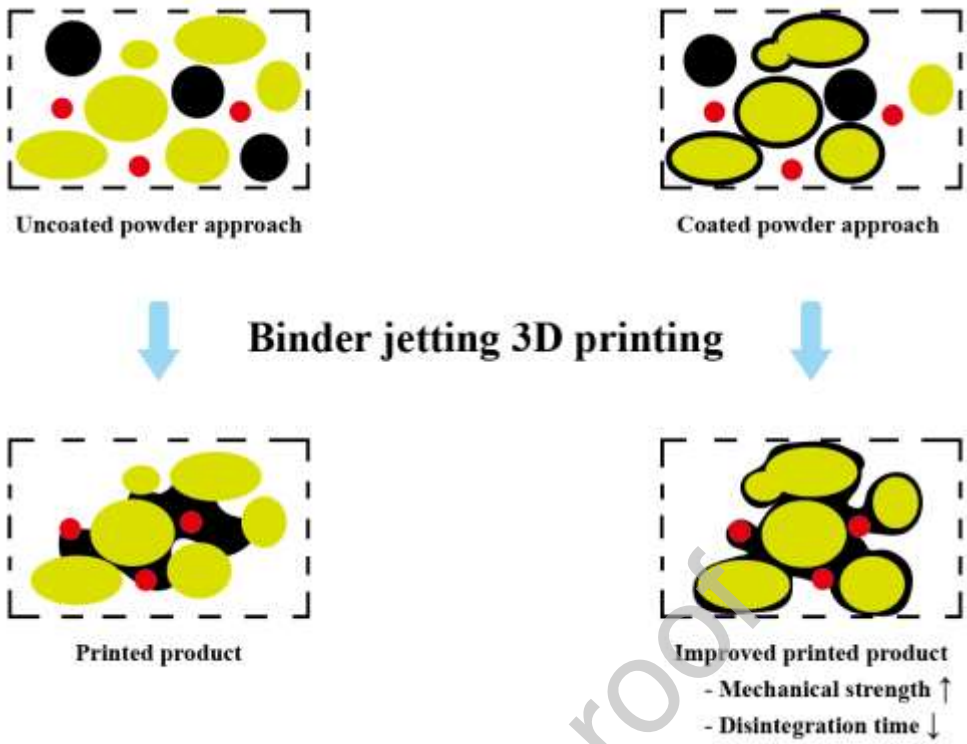

Figure 6 A comparison between the traditional approach of preparing primary powder for binder jetting (BJ) 3D printing by blending of lactose (yellow circles), API (red circles), binder (black circles), i.e., the uncoated powder approach, with the coated powder approach, where pre-treated lactose particles by coating (yellow circles with black outline) were added in the primary powder comprising API, binder and lactose. The latter approach can increase the interparticulate interaction in 3D BJ printing, which improves properties of the printed product.

Journal Pre-proof

Table 1 Compositions of the primary powder for binder jetting. The coated lactose powder comprised lactose and polyvinylpyrrolidone (PVP) at ratio of 19:1.

Sample name	Drug, w/w	Dry PVP, w/w	Uncoated lactose powder, w/w	Coated lactose powder, w/w
P10UC	30%	10%	60%	-
P10C	30%	8%	22%	40%
P15UC	30%	15%	55%	-
P15C	30%	13%	17%	40%
P20UC	30%	20%	50%	-
P20C	30%	18%	12%	40%

Journal Pre-proof

*Table 2 Particle size and size distribution of uncoated and coated lactose powder. Values are presented in mean ± standard deviation, n=3, and the statistically significant difference is indicated with ** p< 0.01 and *** p< 0.001.*

	D10, µm	D50, µm	D90, µm	Span
Uncoated lactose powder	12 ± 1	48 ± 1	104 ± 1	1.90 ± 0.02
Coated lactose powder	16 ± 0	57 ± 1	120 ± 1	1.81 ± 0.00
Significance	***	***	***	**

Journal Pre-proof