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Pharmaceutical applications of powder-based binder jet 3D printing process – A review

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ABSTRACT

Pharmaceutical applications of the 3D printing process have recently matured, followed by the FDA approval of Spritam, the first commercial 3D printed dosage form. Due to being a new technology in the conventional dosage formulation field, there is still a dearth of understanding in the 3D printing process regarding the effect of the raw materials on the printed dosage forms and the plausibility of using this technology in dosage development beyond the conventional ways. In this review, the powder-based binder jet 3D printing (BJ3DP) process and its pharmaceutical applications have been discussed, along with a perspective of the formulation development step. The recent applications of BJ3DP in pharmaceutical dosage development, the advantages, and limitations have further been discussed here. A discussion of the critical formulation parameters that need to be explored for the preformulation study of the solid oral dosage development using the BJ3DP process is also presented.

Contents

Abbreviations: HPMC, Hydroxypropylmethylcellulose; DAMPP, Drop-wise additive manufacturing of pharmaceutical products; API, Active Pharmaceutical Ingredients; 3D, Three dimensional.

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1. Introduction

3D printing (3DP) is a means of printing an object in a layer-by-layer fashion to develop a three-dimensional structure. This printing process can also be known as additive manufacturing, freedom fabrication manufacturing, or additive layer manufacturing. 3DP is widely used in cosmetics, fashion [57], engineering, biomedical, and lately in the pharmaceutical field [63,5]. The advantage of 3DP lies in its versatile ability to develop complex structures in a few steps, an opportunity to personalize medicine [61], and ease of usage [31]. FDA's approval of Spritam—the first commercial 3D printed drug product—has attracted the attention of many pharmaceutical companies Several available 3D printing processes (such as selective laser sintering, fused deposition modeling, or powder-based binder jet 3D printing) are being applied for additive manufacturing of three-dimensional dosage forms. All these printing processes share similar printing procedures and differ by the materials and layering processes used during the process. All 3D printing processes require an image file as a guiding image to initiate the printing process. This image file contains a 3D dimensional picture of the object to be printed. Along with an image file, a 3D printer requires raw materials. For some printing processes, the type of starting materials differs, such as fusion deposition modeling (FDM), where it requires an active pharmaceutical ingredient (API) loaded thermoplastic polymer which melts above a certain temperature ranges and consolidates upon cooling. For some processes, the required type of raw materials is powder, such as selective laser sintering or binder jetting, where a solid material is needed as a base material of the structure, and binding material is needed as a binding agent (binder jetting). A 3D printer contains a nozzle to extrude or spray raw materials and a build platform to build the objects. The material type varies according to the printing processes. 3D printing has been widely applied to dentistry, biomedical engineering, electronics, and cellular engineering. However, the application of 3D printing in the pharmaceutical field has been rising recently. The interest in 3D printing application had peaked in dosage form development when the FDA approved the first 3D printed tablet, Spritam, by Aprecia Pharmaceuticals in 2015. Aprecia utilized the binder jetting 3D printing process to fabricate Spritam (Aprecia Pharmaceuticals, 2020). Recently, Triastek, Inc. received FDA approval on their IND application of a 3D printed dosage form T19 [74]. Other 3D printing methods are being investigated for solid dosage development, but they are still in the research and development phase. 3D printing in pharmaceutical dosage forms come with multiple advantages, such as the opportunity to personalize medicine [23], the ability to develop complex dosage form geometries, prepare high drug loading [35], and the lack of compression step which can open various avenues to different drugs with low compressibility, lower bioavailability and higher drug loading issues. 3D printing (binder jetting) also provides highly dispersible dosage forms, which can surpass the onset time of action as compared to the conventional dosage forms [36]. 3D printing of dosage forms is relatively new to all the other dosage manufacturing methods available in the industry [2]. As a result, the regulatory approval timeline of printed dosage forms is lower than the other conventional methods as there is no current industry draft guidance for specific 3D printing processes [58,45].

The powder-based binder jet 3D printing is based on inkjet printing technology [53]. Hence the names binder jet 3D printing (BJ3DP) and inkjet printing are used interchangeably throughout the paper. There are several research and review articles available on formulation development and pharmaceutical applications of 3D printing. This review article focuses explicitly on BJ3DP technologies that have been extensively explored for dosage form development. Furthermore, this paper delves into more details on the BJ3DP process and its advancement throughout different industries, and later on, focuses on the pharmaceutical application and formulation development aspects of BJ3DP.

2. Binder jet printing process (BJ3DP)

BJ3DP is a powder-based 3D printing process where a binder solution is jetted onto a powder bed, binding it together to develop a 3D printed structure [53]. A BJ3DP system typically comprises a binder solution reservoir to store the binder/ink, a powder reservoir, and a build platform for the printing process [81]. During the printing process, powder discharges from the powder reservoir on the build platform. This step is followed by spreading the discharged powder with a roller in a thin layer on the build platform and subsequently jetting a binder solution based on the image design file of the desired object geometry. Once the first layer is formed, the same powder spreads and the jetting process repeats in a layer-by-layer fashion until the desired object is printed. BJ3DP was originally developed at the Massachusetts Institute of Technology and was patented by Emanuel Sachs [64]. Later, Z corporation commercialized technology that added color capability and dubbed the technology in "3D printing" [53]. BJ3DP has been extensively used in rapid prototyping such as electro-chemical [1], plastic surgery [13], bone scaffolds [82], and the cosmetic industry [76]. The application of BJ3DP in the pharmaceutical industry first received its recognition in 2015 when the FDA approved the first 3D printed tablet fabricated using BJ3DP [35]. Since then, multiple studies have been going on to develop different types of solid dosage forms [73,77] using this printing process,

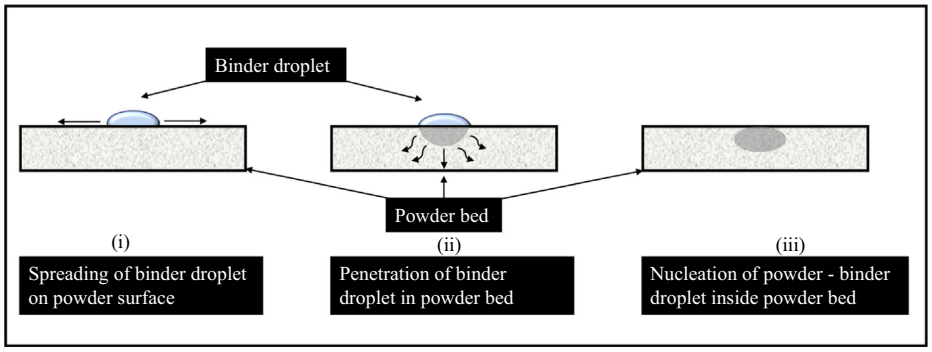

Fig. 1. Powder-binder interaction during BJ-3DP process.

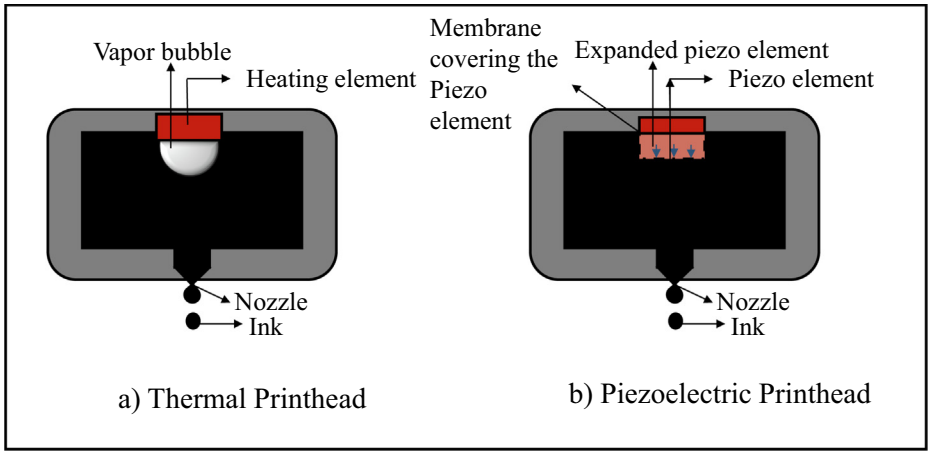

Fig. 2. Printheads commonly used in BJ-3DP process a) Thermal printhead which contains a heater inside the chamber and b) Piezoelectric printhead that contains piezo element both of which cause a pressure build up inside the chambers jetting process.

such as orally disintegrating, conventionally durable tablets [14,67], complex release dosage (ref?)forms, etc.

2.1. Ink jetting process in BJ3DP

BJ3DP is an inkjet printing process where the printer takes a digital image file from a computer and recreates it onto a powder bed using a binder solution [11]. In a printer, binder solution comes from the binder reservoir to the local print head chamber prior to the printing/jetting process. BJ3DP uses the most industrially [59] common drop-on-demand (DOD) printing process where the binding solution is ejected from the print head by reduction of the chamber volume via quasi-adiabatic process (piezoelectric) [70] or by cavitation bubble formation process (thermal). Piezoelectric printhead consists of a piezoelectric element that changes physical dimensions upon receiving an electrical signal resulting in pressure waves inside the printhead chamber and consequently the jetting of ink solution via the nozzle [16]. For thermal printheads [60,17,28], a heating element installed inside the printhead causes bubble formation resulting in positive pressure and jetting of ink during printing due to pressure difference (Fig. 2).

BJ3DP is a printing process where the solid body of the printed object is comprised of powder material and cured binding solution. The printed object is built in a layer-by-layer fashion in this printing process, and thus, the structural integrity depends on the orientation/direction of the printing process, the packing density of the powder mixture, as well as the curing process of the binding agent after the printing. The efficiency of the printing process depends on the jetting accuracy of the binder solution. The four key steps to fabricate printed parts using BJ3DP are: powder dispensing, spreading powder, binder dispensing, and drying of printed parts. The factors affecting these steps can be grouped in three sections: (1) Critical raw material attributes (Printability of powder mixture, Jettability of binder solution and powder-binder interaction) (2) Critical Process parameter (Printing parameter, Orientation of printed objects, and Post-processing) and (3) Critical product properties.

2.2. Critical raw material attributes

As discussed, BJ3DP requires powder mixture and binder solution as raw materials to fabricate printed products. The powder mixture (powder flowability, powder packing density, and particle size distribution) and binder solution (viscosity, surface tension, density, etc.) properties directly contribute to the printed product properties such as mechanical strength, surface finish, etc.

2.2.1. Printability of powder mixture

The powder is one of the important raw materials in BJ3DP that has direct contributions to the printed object property, and most of the composition in printed objects comprises a powder. The powder mixture used in the BJ3DP process needs to have a printability property influenced by the specific properties of the powder. Printability can be defined as the property of powders' essentials to the 3D printing process [Zhou et al.]. Following is some of the critical parameters that govern the printability of a powder:

- Powder specific properties-The ability of the printed layer to remain intact as a subsequent layer of powder is spread on top. The structural fidelity of the printed layer further depends on the powder flowability and packing density of the powder, particle size distribution, etc.
- Powder-binder interaction- The ability of the powder to bind with the binder/ink solution, which is influenced by the specific surface area, wettability, and bindability of the powder [68]. These properties will be discussed in detail in Section 2.1.3.

2.2.1.1. Powder specific properties.

i. Particle size distribution

Particle size distribution has a direct impact on the printed product and an independent property of powder that governs powder flowability and powder packing density in the BJ3DP process. Lu et al. [47] studied the effect of particle size on the 3D printed solid structure and concluded that the particle size of powders directly contributes to the mechanical strength and surface roughness of the printed object. Their work summarizes how a powder bed consisting of lower particle size (<20 μm) can provide higher powder packing density and a low porosity bed, which ultimately offers higher green strength or mechanical strength and a smoother surface to the printed object. Although, this perspective has been contradicted by other research where it shows fine particles cause unnecessary bleaching issues in the printing process [27].

Mostafaei et al. studied the role of particle size distribution on the physical integrity in the printed object. The researchers observed that higher physical integrity for the printed parts could be obtained via higher bed packing density, pore removal, and the final microstructure of the printed parts. Mostafaei et al. also observed that fine powder particles (16–25 μm) produce lower physical strength in the printed parts compared to the medium (16–63 μm) and coarse (53–63 μm) powder particles [54]. Bai et al. found that a mixture of bimodal particle distribution could improve bed packing density and cured density of the printed objects [7]. Compared to a gaussian distribution of powder particle distribution, a bimodal distribution can provide better flowability (bigger particles) and improved bed packing density which contributes to optimized physical integrity in the printed products [7]. In contrast, small particles provide higher densification of the powder bed packing and, finally, higher physical strength in the printed object [19]. Segregation in pharmaceutical dosage form development causes critical failure of the final product because of the content non-uniformity. For polydisperse and cohesive powder mixture, content non-uniformity can occur in solid dosage development by producing several printed dosage forms containing non-uniform API amounts [26]. Thus, particle size distribution remains one of the critical raw material attributes for pharmaceutical dosage development regardless of the manufacturing process.

ii. Powder flowability

Powder flowability is one of the deciding factors to obtain high-resolution printing in BJ3DP, as the printing process involves the layering of several powder layers stacked on each other. A poor powder flow in the printing can cause 1) damage on the print bed by creating particle agglomerates, thus reducing the print resolution 2) Content non-uniformity of API in the printed dosage form. A tablet manufactured using BJ3DP is loaded with API either from the powder or printing ink. Since the API source is the powder mixture, a mixture with poor powder flow possesses a higher risk for uneven distribution of the API and segregation throughout all the printed tablets.

In BJ3DP, the flowability of a powder mixture should be optimized to provide a uniform distribution of the powder, higher bed packing density (to hold the initial printed layer in place while spreading the next layer of powder on top), and good flowability to spread micron size (100–250) layer during powder spreading in printing [7]. Powder mixture consists of larger particles that tend to provide higher flow but are unable to offer higher bed packing density. Comparing to this, the powder mixture with smaller particles contributes to higher bed packing density but displays poor flow. For small particles, inter-particle forces dominantly govern their flow, such as Van der Waal's (VDW) attractive forces along with capillary and electrostatic forces [65]. High VDW forces can significantly reduce the powder flow for smaller particles leading to inconsistent powder spreading during printing.

iii. Packing density

During BJ3DP, a binding solution is applied locally onto a powder bed. Once one layer is printed, the further powder is added to the previous layer to build a printed product. One of the significant challenges is maintaining the spread layer to obtain a printed product with uniformity and maximum density. Uniformity of the packed bed during printing is significantly essential and depends on the packing characteristics, i.e., shape and sizes of the powder particles [40,66].

Lu et al. [47] studied the effect of particle size on powder bed packing density. This study shows for smaller particles (<75 μm) powder packing rate in the printing significantly reduces due to roller spreading process, and with particle size > 75 μm the powder packing rate is similar to the loose random powder packing with the negligible effect of roller speed. Lu et al. finding was corroborated with Zhou et al. [82] work. In this study, Zhou et al. explored the effect of particle size on the bed packing density of the print bed using a binary powder mixture. Their study concludes that a coarser binary powder mixture ($D_{10} \geq 20$ μm) exhibits a significantly higher bed packing density compared to a fine binary mixture ($D_{90} < 20$ μm). The packing ratio for the coarser powder mixture ranges from 30 to 40%, whereas the bed packing ratio of the fine binary mixture was <30%.

While studying the effect of the particle size distribution (PSD) on powder bed packing for BJ3DP, Bai et al. [6] found that a mixture of bimodal powder mixtures improves the powder packing density by ~8.2% compared to the packing density achieved by monosized fine powder mixture (Coarse $D_{50} \sim 75$ μm & fine ~5 μm) where the coarse to fine particle size ratio was kept in between 1:3 and 1:6. Du et al. [20] performed a further investigation and discovered that multimodal (Bimodal or trimodal) powder mixtures could achieve higher bed packing density irrespective of their particle sizes. Such as, both a lower particle size ratio (fine to coarse) and a larger packing density ratio (fine to coarse) led to achieving maximum bed packing density.

Similarly, Averardi et al. [4] reviewed the effect of layer thickness and PSD on the powder bed packing density and consequently found that thin powder layer printing provides lower bed packing density while thick powder layer can provide 30% to 70% of powder bed packing density. This review also mentions that bimodal distribution can provide higher bed packing density and provide higher interaction with the powder and the binding agent, thus providing higher print resolution.

Powder bed packing density affects not only the mechanical strength or the print resolution of the printed product it also affects the post-processing step of BJ3DP. A higher bed packing density causes lower porosity in the print bed, reducing the thermal conductivity during the drying process. However, having a

higher porosity can be beneficial for insulating powder particles as the convective and radiative heat transfer can be increased. As contradictory requirements exist for bed packing density, the optimized properties of the packing density depend on the application of a printed product, such as for pharmaceutical application purposes, lower porosity in powder is desirable if designing a swallowable tablet [67]. Whereas, for orodispersible tablet dosage form higher porosity in the printed tablets are needed for quick disintegration [38,27].

2.2.2. Jettability of binder solution

Printing efficiency in the inkjet printing process depends on resolution, drop placement accuracy, and the ink/ binder solution [28]. Resolution and drop placement accuracy are printing process parameters discussed in the relevant Sections 2.2.1. Consistency, however, a significant parameter for defining printing efficiency, is a function of fluid (binder solution) properties such as jettability.

Jettability or printability of binder solution can be defined as the ability of the ink to generate a stable and single drop on impact once it reaches the print bed [18]. The jetting process during printing occurs by a drop generation process, which maintains reproducibility in droplet formation during the binder jetting process, and the ink solution needs to have optimum jettability [48].

The drop generation in DOD printheads is a complex process and is subjected to extensive research [21]. Drop generation occurs via jet breakup behavior of the fluid, first studied by Leonardo da Vinci in the Codex Leicester. The jet breakup behavior of fluid stays the same regardless of the nozzle length or the nature of perturbation acting on the jet [10]. The parameters responsible for controlling the break-up behaviors are surface tension, viscosity, droplet velocity. This drop generation/jet break-up process can produce either stable or unstable droplets depending on these fluid properties.

During a drop generation process, the main drop is generated along with satellite droplets. A stable droplet is formed when the satellite droplets merge with the main drop before it hits the print bed. Whereas unstable drop formation produces either a larger amount of satellite droplets that are unable to merge as the main drop lands on the print bed or cannot generate any drop, thus reducing the print resolution.

This drop formation behavior of fluid/ink can be governed by few dimensionless parameters such Weber no (We), Reynolds no (Re), and Ohnesorge no (Oh) (Eqs. (1)–(3)) [28].

$$Re = \frac{v\rho a}{\eta} = \frac{inertial\ \ forces}{viscous\ \ forces} \tag{1}$$

$$We = \frac{v^2\rho a}{\gamma} = \frac{inertial\ \ orces}{surface\ \ forces} \tag{2}$$

$$Oh = \frac{\sqrt{We}}{Re} = \frac{viscous\ \ forces}{surface\ \ and\ \ inerial\ \ forces} \tag{3}$$

where v is the velocity and a is the characteristic length equal to the nozzle diameter in this case, and γ, ρ, and η are the density, dynamic viscosity, and surface tension of the ink solution, respectively.

Fromm [24] characterized this fluid behavior using another parameter, Z, which is 1/Oh. Fromm proposed that the fluids of Z > 2 are able to produce stable drops or are jettable. As represented in Fig. 3, the parameter $Z = 1/Oh$, which is the reciprocal of the dimensionless parameter, or Ohnesorge number, has been found experimentally to be correlated with the jetting behavior. Derby, later on, proposed another range of stable drop formation using numerical simulations and, i.e., 10 > Z > 1. For $Z < 1$, viscous forces dominate, preventing drop ejection, whereas, for $Z > 10$, more significant satellite drops are formed, thus causing unstable drop generations [18]. These dimensionless parameters can be calculated by measuring the surface tension, viscosity, binder droplet velocity, and density of each binder solution. The quantification of the jetting process for the binder solution is critical as the reproducibility of the jetting solely depends on whether or not the binder solution is in the printable/ jettable zone (Fig. 3).

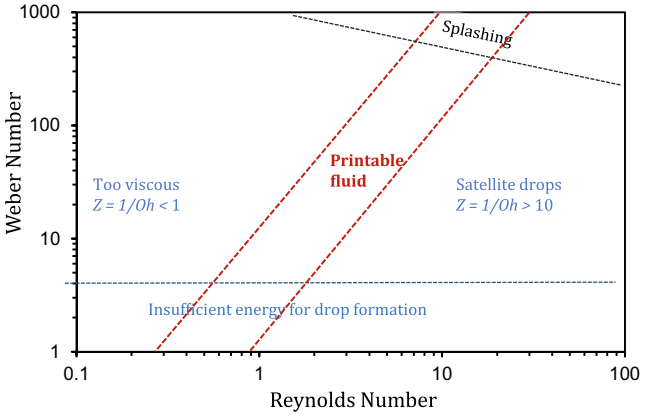

Fig. 3. Printable Zone for ink solution. Reproduced from [18]to describe the region of printable fluid for BJ3DP. To have a jettable binder solution in BJ3DP the Z value of the binder solution should lie in between the printable fluid zone not overlapping with Splashing or insufficient energy to drop formation zone.

The binder solution used in the pharmaceutical field in BJ3DP contains one or several solutes (polycaprolactone, different grades of polyvinylpyrrolidone (PVP) (such asPVP K25, PVP K17, and PVP K30), ethyl cellulose (EC), poly-L-lactide (PLLA), etc.) that are either dissolved or dispersed in a solvent medium (such as- Ethanol, Chloroform, Acetone, Water, and Buffers) [27]. Both the solvent medium and the solutes used in the binder solution of BJ3DP have been varied depending on formulation requirement.

2.2.3. Powder-binder interaction

BJ3DP occurs by depositing binder ink solution on top of a powder bed according to a 3D model design. Once a droplet comes in contact with the powder bed, it spreads and penetrates the powder bed and thus producing a granule embedded in a loose pack powder bed (Emady, 2011) (Marston, 2013). These granules work as a building block where further deposited binder droplets attach these granules throughout the printing process to develop a 3D printed product. The interaction between the binding ink and powder is known as material compatibility [8], is governed by two properties:

(i) Wettability – Wetting behavior of the binder solution on the powder bed. As the binder reaches the print bed during printing, it spreads and penetrates the powder bed vertically and laterally [30,46]. Depending on the wettability of the powder, the shape of the printed part is defined. Binder saturation is a parameter that can be calculated to define the total amount of binder need to be jetted per printed part depending on the powder bed density, the diameter of the printed object, and powder layer thickness used in the printing. It has been observed that 70% binder saturation is optimum to reach the maximum densification of printed parts [22]

(ii) Bindability- Ability of the binder solution to bind the powder based on interparticle forces [66]. Binding event occurs between powder and binder solution predominantly though incorporation of adhesive and cohesive forces in between them. Bindability can also be defined as the amount of pow-

der that is bound with a specific amount of binder. Depending on bindability properties the combination of binder solution and powder mixture is selected for BJ3DP process as the binding powder in between them mostly decides the mechanical strength of the printed tablets [62,66,29].

Bai et al.[8,68] developed a benchtop test by studying the powder binder interaction in BJ3DP and proposed an experimental approach that can be used as a platform for material screening and optimization of the printing process parameters. This experimental approach based on sessile drop goniometry on a powder substrate coupled with models of capillary flow provides a fundamental understanding of powder binder interaction. Sen et al. modified an existing screening test/drop test used for wet granulation in the pharmaceutical industry. They established it as a prescreening test for BJ3DP of pharmaceutical dosage form using statistical analysis [68].

As the binder droplet impacts the powder bed, it creates a contact angle with the powder surface based on the wettability property of the binder (Spreading). Once the droplet comes in contact with the powder bed, the pores in the bed act as capillary tubes and starts absorbing the droplet liquid inside the powder (Penetration) (Fig. 1). The contact angle formed between the binder droplet and powder surface during BJ3DP can be considered a dynamic contact angle. It includes the spreading (advancing contact angle) and penetration (receding contact angle) behavior of the binder liquid. The dynamic contact angle can be calculated by calculating Capillary number or Ca, which depends on viscosity (μ), velocity (v), surface tension (γ_{LV}) of the binder droplet. While it is difficult to calculate the dynamics contact angle from powder bed sessile drop goniometer, it can also be measured by measuring the drop penetration time. As Capillary force (Ca) is the main driving force for the binder penetration in the powder bed using the Washburn model, the dynamic contact angle can be measured with the help of Eqs. (4) and (5) [8] by measuring binder viscosity, surface tension, powder particle size, powder bed packing density, binder droplet volume and binder penetration time.

$$Ca = \frac{\mu v}{\gamma_{LV}} \tag{4}$$

$$\cos\theta_d - \cos\theta = \sqrt[a]{Ca} \tag{5}$$

where a is an empirical factor.

So far, most of the studies regarding powder binder interaction in the BJ3DP field are performed in the biomedical, cosmetic, and aero engineering industries. The printed part's mechanical strength (bindability) took place by powder binder reactivity [82]. However, in the pharmaceutical field, the mechanical strength of the printed part in BJ3DP mostly depends on solid bridges, polymeric chain interaction, and Vander Waals forces [66,53]. Nevertheless, the fundamental interaction of the wettability properties of the binder solution remains the same regardless of the bindability properties.

The steps involved in the powder-binder interaction during printing are as follows- i) Spreading of binder/ink droplet on top of the powder bed ii) Penetration of the binder drop into the powder bed. iii) Agglomeration/binding of the powder with the binder [82]. The mass formed out of the interaction is called agglomerates [66] or primitive [8], and these agglomerates work as a unit building block of the printed parts. To develop a printed part in layer-layer fashion using BJ3DP, these agglomerates are overlapped with each other across each layer and sewn throughout the printed layers [7]. Thus, the shape and morphology of these agglomerates can help optimize necessary printing process parameters to predict mechanical strength and the shape of the printed parts, such as 1) spacing of the drops on the powder bed (DPI-dot per inch), 2) Layer thickness. DPI, layer thickness, and the volume of the binder droplet also provide binder saturation ratio (total amount of binder over total pore volume of the printed parts), that can successfully provide the exact composition of the printed part, which is an important parameter while fabricating dosage form (2.2). Miyanaji et al. [52] developed a mechanistic model to predict the optimal binder saturation level that can be attained in the printed parts. He established this model based on capillary pressure estimation caused in between binder droplet and powder on the bed at equilibrium state during the printing process. This work also concludes that binder saturation strongly depends on the binder droplet and powder bed interaction, including spreading and penetrating.

2.3. Critical process parameters

2.3.1. Printing parameters

Printing parameters such as roller speed, powder layer thickness, binder saturation ratio are critical to providing optimized printing in a BJ3DP process. Such as, for an overfed powder bed, the low roller can lead to dragging. Also, higher thickness in the powder layer lowers the printing resolution and provides lower binder saturation which can lead to producing poor physical integrity in the printed parts [7].

2.3.1.1. Binder saturation and layer thickness. Binder saturation ratio and layer thickness combined have a significant effect on a printed product fabricated using the BJ3D printing process. In the BJ3D printing process, these parameters can be controlled to optimize the mechanical strength of the printed parts. With decreasing layer thickness, the binder droplet can quickly reach the previous wet layer. Although the vertical penetration of the binder droplet gets pushed back by the previous wet layer, the spreading of the binder in the lateral direction remains uninhibited, causing a higher spread in the lateral direction of the printed specimen while decreasing the layer thickness. While under constant layer thickness lower binder saturation ratio provides minimal spreading of binder in the lateral directions.

Vaezi et al. [75] studied the effect of layer thickness and binder saturation on the mechanical strength of the printed product. Their study shows that under the same binder saturation lowering layer thickness of ZP102, powder (powder made by Zcorp and calibrated on Zcorp binder jet 3D printer) increases the tensile strength in the printed parts. Under the same layer thickness, the 90% binder saturation ratio provides lower tensile strength and integrity than 125% binder saturated printed parts. Enneti et al. [22] have also found that the binder saturation and powder layer thickness directly affect the green strength of the printed products made by WC-12 %Co powders. WC-12 %Co is tungsten, carbide-cobalt-based powder suited for the fabrication of high-density parts with binder jetting 3D printing process. Increasing powder layer thickness decreases the mechanical strength, where increasing binder saturation under constant layer thickness increases the mechanical strength of the printed products. Chen et al. and Miyanaji et al. explored the optimal process parameters of the BJ3DP process by optimizing layer thickness, binder saturation ratio in the printing process [15,50,51]. Chen et al. observed that layer thickness has a significant effect on the surface roughness of the printed parts. Whereas, Miyanaji et al. noted that increasing binder saturation level from 50% to 75% would increase the physical strength of the printed parts by 50%.

2.3.1.2. Roller/Spreader speed. The spreading occurs during the printing process to spread powder on top of the pre-printed layer by using a roller/spreader. The roller speed contributes to the accuracy of the printed parts horizontally. The higher the speed of a roller, the lower the contact time of the roller with the powder

bed, resulting in minimized contortion of the powder bed by the roller laterally. Miyanaji et al. explored that increasing the roller speed from 2 to 6 mm/s increases the accuracy of the printed part in the lateral direction [51].

2.3.1.3. Printing speed. The printing time in BJ3DP can be decreased by increasing either number of print cycles in a printer or by increasing the speed of the printheads navigating across the print bed. However, increasing the printhead speed may affect the printing resolution or shape accuracy. As with higher printing speed, liquid binder solution might not evaporate properly from the pre-printed layer before the next layer is printed, leading to higher surface roughness, lower-dimensional accuracy, or smearing of the pre-printed layer during the printing process. Myers et al. [55] had found that the mechanical integrity of a printed part and reproducibility of the printing process decreases along with increased surface roughness with higher printing speed.

2.3.2. Orientation of printed objects

Orientation of the printing process plays a significant role in contributing to the mechanical strength of the printed parts [66]. The plausible reason for the mechanical strength variation arises from the non-uniform dispensing of the powder and binder solution, optimal towards the printing direction [53]. With increasing printing speed, the un-even dispensing of raw materials worsens, and printing accuracy decreases.

2.3.3. Post-processing

After a successful printing process in BJ3DP, the printed parts need to go through a post-processing step. Post-processing for BJ3DP consists of three phases.

2.3.3.1. Curing. Curing of BJ3DP parts takes place along with the surrounded powder to remove the excess binder solution from the print bed [32,35] and to increase the mechanical strength of the printed parts. The print bed is directly removed from the printer for the curing process and moved to a dryer. Once the binder is dried and the mechanical strength printed part is optimized, the parts are moved to the dedusting station. The parameter of curing process such as temperature and duration of curing depends on the final properties of the printed parts.

2.3.3.2. De-powdering/De-dusting. Dedusting/de-powdering is a process to remove excess surrounding powder of the BJ3DP part after the curing process. Dedusting is performing mainly by vacuum [7], manual brushing, or physical sieving process [67]. The rest of the dedusted loose powder can be recycled depending on the quality standard of the printed products.

In the pharmaceutical industry use of recycled powder in BJ3DP has been considered with caution.

According to the Food and Drug Administration (FDA) draft guidance 2016, "Technical Considerations for Additive Manufactured Medical Devices", FDA establishes few control parameters on the reusing process of recycled powder such as "filtering reused material, a limit on the percent of reused material, or monitoring for changes in chemistry, oxygen, or water content". Wang et al. and Wilts et al. has successfully explored the possibility of reusing recycled powder by using biodegradable polymer such as ethylcellulose, maltodextrin, microcrystalline cellulose, lactose, etc. [78,79].

2.3.3.3. Densification. Densification or sintering process typically takes place to increase the mechanical strength of the printed parts. After curing and de-dusting, the printed parts are solely held together by the binder material within the powder particles [7]. This process can be carried out by i) infiltration [25] and ii) sintering [44,56]. The densification process has been the least explored step in the application of BJ3DP in the pharmaceutical field of the dosage form as dosage form rarely requires higher mechanical strength acquired by densification [38]. However, in biomedical printed bone, the scaffold goes through a rigorous densification process depending on the required strength.

2.4. Critical product properties

2.4.1. Mechanical strength

Mechanical strength or green strength of the printed product using BJ3DP is of particular interest as the whole mechanical integrity of the printed parts solely depends on the forces acting in between the powder particles and binder materials. Thus, the mechanical strength of the printed product significantly depends on the raw material properties (Powder packing density, PSD flowability, and jettability of binder solution) and process parameters (Printing parameters, Orienting of printed product, and post-processing steps).

2.4.2. Surface finish

For printed materials using any powder bed printing process, including BJ3DP, the particle size distribution of the powder and the layer thickness has a direct effect on the surface roughness of the finished product. Smaller particle size and lower layer thickness produce better surface compared to coarse particles and higher layer thickness.

2.4.3. Dimensional accuracy

According to the Food and Drug Administration (FDA) draft guidance 2016, "Technical Considerations for Additive Manufactured Medical Devices", FDA recommends to compare the desired feature size of the printed product to the minimum possible feature size for the respective printing process and manufacturing tolerance of the the individual printer (CDRH, n.d.). Dimensional specification of the final product should be documented for printed tablet using BJ3DP as the printed tablets are freely form fabricated products with die cavities unlike conventional tablet dosage forms.

2.4.4. Disintegration time

The Zipdose technology from Aprecia using BJ3DP provides orodispersible tablets (ODTs) with a higher dose upto 100 mg, which disintegrates in seconds. To ensure minimizing batch to batch variability of the printed tablets disintegration time should be observed as a in process testing parameter.

While BJ3DP has been used in a large scale to produce ODTs producing modified released tablets using large manufacturing scale with acceptable repeatability might pose a greater challenge, as the modified released tablets would have denser structure compare to ODTs. By varying the bed packing porosity of the powder bed and or by varying the binder concentration in the ink solution the release profile can potentially be achieved. However, higher binder concentration can probably slow down the curing process which will rise other concerns such as removal of residual solvents.

For pharmaceutical dosage form development using BJ3DP, the significant product/dosage properties are mass, Loss on drying (LOD), hardness or mechanical strength, disintegration time etc. From formulation development point, irrespective of conventional/printing manufacturing, in any batch manufacturing process, random unit dosages are selected according to US Pharmacopeia (USP) guidelines (USP, 2011) which go through certain dosage characterization for a batch to have passed acceptance criteria such as mass, LOD or moisture content and hardness or mechanical strength and disintegration time to minimize batch to batch variability.

3. Pharmaceutical application of binder jet printing process

The Binder jet 3D printing process has been applied extensively for dosage development since the FDA approval of the first 3D printed dosage form, SPRITAM. The binder jet printing process holds numerous advantages over other printing processes in dosage form development such as –

- A variety of powdered materials can be used for printing if the right binding agent is used.
- The inkjet process operates at near room temperature, which is desirable for handling heat-sensitive APIs.

Binder jet 3D printing process enables fabrication of complex geometry down to millimeter scale, which is otherwise difficult to achieve using conventional manufacturing. The ability to develop complex geometry with this 3D printing process has recently extended to the fabrication of biomaterials as scaffolds in the bone tissue engineering field. Butscher et al. [12] studied the printability of calcium phosphate powders for scaffolding bone tissue. Zhou et al. [82] came up with an intricate scaffold design to optimize cell proliferation and enhanced cell adhesion. Inzana et al. [34] optimized the formulation of bone scaffolds to increase the mechanical strength and cell viability in the printed product. The current application of the BJ3DP process has been more focused on pharmaceutical dosage manufacturing. The pharmaceutical dosage form here mainly represents solid oral dosage containing API and other excipients. Unlike conventional solid oral dosage manufacturing (such as direct compression and dry granulation) in the BJ3DP process, API can be added to the tablet using two following approaches [73].

3.1. API in ink approach

(i) Rapidly dispersible tablets- Lee et al. formulated rapidly dispersible dosage form using Theriform/BJ3DP process, using Captopril in ink along with PVP 25 and aqueous buffer [43]. The powder excipient mixture used in this study constitutes maltitol, maltodextrin, polyvinyl pyrrolidone. Sen et al. [67,69] fabricated a rapid release tablet dosage form using BJ3DP incorporating Amitriptyline HCL in ink and lactose monohydrate, microcrystalline cellulose, and PVP K30 in the excipient mixture.

(ii) Delayed-release-Katstra et al. [39] successfully developed delayed-release oral dosage form by varying polymer content (Eudragit 100, Eudragit RLPO) in the binder solution from 8.9 to 17.9%, printed on top of microcrystalline cellulose and spray dried lactose powder bed.

(iii) Zero-order release-Wang et al. [78] developed a zero-order release tablet using BJ3DP by incorporating pseudoephedrine hydrochloride API in ink and Kollidon SR, hydroxypropylmethylcellulose as powder mixture.

(iv) Controlled release tablets-The first pharmaceutical tablet using BJ-3DP was fabricated in 1996. Wu et al. [80] developed a control released tablet using methylene blue and alizarin yellow as a model drug. Apart from the drug, the formulation also contained polyethylene oxide, polycaprolactone as powder excipients, and dichloromethane and chloroform as the binder solution. Due to the toxicity and difficulty in removing binder traces from the formulation, it was considered unsuitable. However, this paper was considered a significant milestone, as 3D printing in the pharmaceutical industry started rising after this study.

3.2. API in powder approach

So far, BJ3DP has been applied in developing several types of tablet formulations, and a few of those formulations are discussed here in the following sections. Table 1 represents a few examples of different types of dosage forms that have been fabricated using the BJ-3DP process with the API in the powder.

(i) Orodispersible tablets-The first commercially available FDA-approved 3D printed tablet Spritam is fabricated using the BJ3DP process [35]. Aprecia Pharmaceuticals patented the formulation of an orodispersible tablet where the drug, i.e., levetiracetam, was incorporated with API in powder approach. ODT products typically are limited by: (i) low drug loading and (ii) slow disintegration. Spritam overcame these two main challenges by enabling: (i) a higher drug loading of (up to 1000 mg), which is higher than what is achievable using a conventional manufacturing process, and (ii) fast disintegration. - Compare to conventional orodispersible tablets (~3 mins) (WHO Tablet Monograph, 2011)(USP NF, n.d.), Spritam disintegrates in ~11 secs, thereby improving the timeline of onset of action.

(ii) Oral Disintegrating tablets- Tian et al. 2018 [36,71] formulated oral disintegrating tablets of warfarin sodium with the drug being present in the powder mixture of D-sucrose, pregelatinized starch, povidone K30, microcrystalline cellulose, and silicon dioxide. The study utilized ethanol as the moistening agent filled into the ink container of the 3D printer. They further evaluated the tablets for various tests such as dose uniformity, hardness, friability, and dissolution. The tablets doses of 3, 2, and 1 mg showed an average disintegration time of 50.0, 35.7, and 11.0, respectively. Moreover, hardness and friability were observed to agree with the required standards, and tablets had uniformly tight structure and smooth appearance.

Table 1
Enlisted research work with drug in the powder mixture solution using inkjet technology.

Formulation Type	Powder bed	Binder/Ink	API	Reference
Orodispersible tablets	Microcrystalline cellulose (MCC), glycerin, Tween 80, povidone, sucralose	Water	Levetiracetam	[35]
Oral disintegrating tablets	D-sucrose, pregelatinized starch, povidone K30, MCC, silicon dioxide	Ethanol	Warfarin sodium	[36,71]
Fast disintegrating tablets	Lactose, PVPK30, Mannitol, Colloidal Silica	Methylene blue (0.5%, w/v) and PVP K30 (5.0%, w/v) in 75% (v/v) of ethanol in water	Acetaminophen	[81]
Complex tablets with Zero order release	HPMC E50, PVP K30, and colloidal silicon dioxide	4.0 (w/v) % EC in 90 (v/v) % Ethanol	Acetaminophen	[83]
Fast Dissolving tablet	Calcium sulphate hemihydrate, PVP VA64, Lactose, Sodium Croscarmellose	Water Hydroxy propyl cellulose, PVP VA64, Hydroxy propyl methylcellulose	Indomethacin	[14]
Novel Doughnut shaped tablets	Hydroxypropyl methylcellulose and ethyl cellulose	Ethanol	Acetaminophen	[81]

(iii) Fast Disintegrating tablets- It is also possible to create tablets with regions of different strengths using the 3D printing process. Yu et al. [81] used thermal printheads, each with four spray nozzles. The powder was composed of acetaminophen, lactose, PVPK30, mannitol, and colloidal silica, and the binder solution was methylene blue (0.5% w/v) and PVPK30 in 75% of ethanol in water. Compared to conventional tablets manufactured using a single punch press, the 3D printed tablets showed an acceptable hardness of 54.5 ± 4.2 N/cm2 with a total mass loss during the friability test being 0.92 ± 0.14%. The tablets were designed with a stronger top and bottom with loose powder inside the tablets to increase hardness and decrease friability. The loose powder inside the tablet offered fast disintegration leading to faster dissolution by increasing the surface area, with 97.7% of the drug was released in the initial 2 min.

(iv) Complex tablets- Yu et al. [83] fabricated complex tablets with zero-order release characteristics by incorporating drugs in the powder bed to increase drug load in the final formulation and release retarding material in the binder liquid or ink. Acetaminophen was employed as the model drug and 4.0 (w/v) % EC in 90 (v/v) % ethanol as the binder liquid. To incorporate retarding effect, sodium lauryl sulfate (SLS), stearic acid (SA), ethyl cellulose (EC), and Eudragit RS-100 were added into the HPMC matrix tablets. The mechanism of drug release from tablets was erosion, with the most retardant effect shown by Eudragit RS-100. Moreover, the tablets showed an acceptable hardness of 73.82 ± 5.47 N/cm^2, which could be due to the presence of EC. The study showed the feasibility to manufacture complex dosage forms by adding drugs in a powder mixture to increase drug loading, which is difficult to achieve by loading drugs in ink.

(v) Fast dissolving Tablets- Chang et al. [14] formulated indomethacin-laden pharmaceutical dosage form by incorporating the API in the powder mixture. The excipient mixture used in the formulation contains Lactose, PVP VA64, sodium croscarmellose, and calcium sulfate hemihydrate. The six liquid binder solutions used in the study contained hydroxypropyl cellulose, PVP VA64, hydroxypropylmethylcellulose, etc. The drug loading of the printed tablets was 5%, and the hardness of the tablets range from 25 to 150 N. Infanger et al. [33] studied the mechanical strength of the printed tablets by varying solid binder grades in the powder mixture. It is shown that the friability of the printed tablets differs from the particle size of the binders.

(vi) Novel Doughnut shaped tablets-3D printing offers the advantage of fabricating tablets of various shapes and desired release. Yu et al. fabricated a novel doughnut-shaped multi-layered drug delivery device with local variations of poorly water-soluble drug and release retardant material to give linear release profiles [81]. They employed acetaminophen as the model drug with hydroxypropyl methylcellulose as matrix and ethyl cellulose as the release retardant material. The binder solutions were formulated using binder I (2.0% (w/v) of EC in 90% (v/v) of ethanol in water) for the top layer and bottom layer and binder II (10.0% (w/v) of APAP in (v/v) 90% ethanol in water) for the middle layers. This shows that 3D printing offers new approaches for fabricating complex dosage forms.

4. Advantages vs. challenges

BJ3DP offers various advantages in pharmaceutical manufacturing, such as:

4.1. Fast dissolving tablets

As BJ3DP produces porous tablet structure leading to fast dissolving tablet resulting in diffusion rate-limited drug delivery and providing a quick onset of action compared to conventional tablet dosage form [84].

4.2. Complex geometry

The 3D printing process, including BJ3DP, provides a technical edge by producing complex geometries that can be translated to design different release profile dosage forms. BJ3DP can print complex geometry objects with dimensions ranging from meter to mm scale. A concept named "in cavity" printing has also been adopted by Aprecia Pharmaceuticals, providing a new opening to complex geometry dosage form using BJ-3DP [3,42].

4.3. The precision of drug loading

Drug loading can be defined as the amount of drug-loaded in one dosage form. BJ3DP possesses the advantage of incorporating drugs or API onto the dosage forms in two ways. a) Adding drug in the powder - It can be used for higher loading. As this manufacturing process does not have a compression step, an incompressible drug such as Paracetamol, Levetiracetam [35] can be loaded to a higher scale (almost 100% to the tablet weight). The precision of drug loading at a higher loading percentage is much easier and achievable as the higher the drug concentration in the powder mixture, the lower the variation in content uniformity. b) Adding drugs in the ink solution- can be used for lower drug loading [85]. Due to the sensitive inkjet printing process, the accuracy of the drug-loaded printing is higher [67] compared to conventional tablet manufacturing and would be suitable for low drug loaded formulation where content uniformity is a big issue, such as Levothyroxine (Shah et al., 2010).

4.4. Solid amorphous dispersion

BJ3DP has shown the possibility to produce solid amorphous dispersion of crystalline materials (model drug) [72], which would help develop formulation with poorly soluble drugs [81].

4.5. Scalability

BJ3DP offers easy scalability compares to the conventional manufacturing process. By increasing printhead inkjet nozzle numbers and building envelope, the amount of printed object production can increase [44].

4.6. Personalization of drug products

BJ3DP allows personalized dosing of API in the drug product. This allows customization for geriatric and pediatric patients. Complications of drug interactions/over-dosing can be avoided by personalization of drug doses [37,57].

4.7. On-site and on-demand preparation

BJ3DP allows on-site manufacturing at the bedside. Thus, this on-demand preparation reduces the time required for the appropriate personalized drug product to reach directly to the patients [5,72].

BJ3DP comes with some challenges as well, and some of them are listed below:

4.8. Drying

It is essential to have a drying/post-processing step after the printing process to remove residual solvents and improve the physical strength of the dosage forms, which could be challenging for the APIs or powder components, which are temperature sensitive. Moreover, certain post-printing processes need to be completed, such as removal of excess powder, which leads to significant wastage of powder, making the process less economical [9]. Reuse and recycle of powder are possible but calls for extreme caution as the processing history may negatively impact product quality and safety.

4.9. Powder layer thickness

The 3D printing process is also controlled by the powder layer thickness and limited by the powder particle size, making it challenging to achieve very high resolution [86]. The layer thickness depends on the packing ability of the printed powders. It is one of the critical parameters that determine the quality of the printed tablets [22].

4.10. Mechanical strength

The application of inkjet 3D printing is also limited to dosage forms of low mechanical strength and high friability[71,81]. Therefore, this process is not ready to be used to make conventional tablets with higher mechanical strength.

4.11. Formulation selection

It is essential to select suitable powder excipients and binders during the development phase, which requires thorough screening [81] and a detailed understanding of the materials and the 3D printing process [71]. For example, the binder should have sufficiently low viscosity to be ejected from a small nozzle, and the binder must dry relatively fast without clogging the print nozzles so that the next powder layer can be applied. In addition to that, the powder should have high flowability, which is always not possible to achieve.

4.12. Regulatory challenges

3D printing is gaining popularity in the pharmaceutical industry. Still, there are no clear regulatory guidelines for manufacturing pharmaceutical dosage forms, and guidelines on 3D printing to operate within the regulatory framework are still under development, making it difficult to manufacture 3D printed drugs. Also, the BJ3DP process is still in its nascent stage, and numerous steps in the manufacturing process still need to be optimized. Moreover, the primary advantage of 3D printing in pharmaceutical dosage form manufacturing is producing personalized medicine. There is no regulatory structure that could be applied to dosage forms made in this manner. There are draft guidelines issued by FDA in 2017, which have certain considerations for Additive Manufactured Medical Devices [49]. The idea of personalized medicine is to make dosage forms in setting such as hospitals which are regulated under the section 503B(b)(5) and section(a)(10). Still, these sections do not mention 3D printing for compounding the dosage forms [41]. The optimization of the post-processing step also needs to be carried out for each formulation, which can be an added step and not economical for industrial-scale manufacturing. There could be multiple steps in 3D printing manufacturing which are affected by the 3D printing method being used, and these steps are different than the steps used during conventional manufacturing. This indicates that each step should be controlled differently, which further complicates the regulatory control of 3D printing. Nevertheless, the regulatory approvals of 3D printed dosage forms are increasing, such as Triastek received Investigational New Drug (IND) approval for its first 3D printed drug product, T19, from FDA in 2021. T19 was printed using Melt Extrusion Deposition (MED) to treat rheumatoid arthritis (3D Printing Industry, 2021).

5. Conclusion

BJ3DP is a promising technology in pharmaceutical dosage form manufacturing with its leading advancement in the pharmaceutical field. In this paper, a comprehensive literature review on the BJ3DP process has been carried out. BJ3DP has been applied primarily in engineering, cosmetic and biomedical industries and very recently in pharmaceutical dosage manufacturing. The application of BJ3DP in the pharmaceutical industry has achieved a substantial milestone after the FDA approval of Spritam. The future potential application of BJ3DP has expanded from clinical trials to personalized/tailored dosage forms. The field of BJ3DP is rapidly evolving and will continue to enrich with new research, new possibilities as well as new perspectives.

Regardless of its success, the knowledge about the application of BJ3DP in pharmaceuticals is still at its emerging stage. Before assimilating 3D printing as a mainstream medicine manufacturing process (such as the conventional tablet manufacturing process), there are several steps of process understanding need to be made. The formulation development steps involved in BJ-3DP still need to be optimized to attain a reliable source for high-quantity production in competing with the conventional dosage form. However, the advantages of the BJ3DP outweigh the disadvantages and cannot be ignored.

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.

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