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A novel fast disintegrating tablet fabricated by three-dimensional printing

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Abstract

Background: Based on computer-aided models, three-dimensional printing (3DP) technology can exercise local control over the material composition, microstructure, and surface texture during it layer-by-layer manufacturing process to endow the products with special properties. It can be a useful tool in the development of novel solid dosage forms. *Method*: In this study, a novel fast disintegrating tablet (FDT) with loose powders in it was designed and fabricated using 3DP process. The inner powder regions were formed automatically by depositing the binder solutions onto selected regions during the layer-printing processes. *Results*: Environmental scanning electron microscope images clearly showed that the printed regions were bound together. The particle size was reduced or individual particles could no longer be distinguished. In contrast, the unprinted regions were uncompacted with cracks and fissures among the loose powders. The tablets had a hardness value of 54.5 N/cm^2 and 0.92% mass loss during the friability tests. The disintegration time of the tablets was 21.8 seconds and the wetting time was 51.7 seconds. The in vitro dissolution tests showed that 97.7% acetaminophen was released in the initial 2 min. *Conclusion*: 3DP process is able to offer novel methods for preparing FDTs.

Key words: *Binding mechanisms; fast disintegrating tablet; inner structure characteristics; mechanical performance; three-dimensional printing*

Introduction

Fast disintegrating solid dosage forms have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry because of the advantages of easy administration to patients who have difficulty swallowing, more rapid drug absorption, patient convenience, and improved patient compliance[1,2]. The popularity and usefulness of the formulation resulted in the development of several related technologies and processes such as lyophilization, molding, sublimation, compaction, TheriForm™ process, rotary process, and additional technologies for improving fast disintegrating/dissolving properties including spray drying, moisture treatment, sintering, and taste masking[3–5].

The key properties of fast disintegrating tablets (FDTs) are fast absorption or wetting of water into the tablets and disintegration of associated particles into individual components for fast dissolution. This requires not only that excipients should have high wettability, but also that the tablet structure should have a highly porous network[3]. When conventional direct compression and granulation methods are employed, the porosity of the tablets is inversely related to the compression pressure. However, high compression pressure is needed to ensure adequate strength of the tablets. Thus, it is often difficult for the tablet to have porosity that allows fast water absorption while maintaining high mechanical strength. New strategies to increase tablet porosity without sacrificing its mechanical performance are desired[1,2].

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Three-dimensional printing (3DP), a rapid prototyping technology, was first developed at the Massachusetts Institute of Technology in 1992[6]. Based on computer-aided design (CAD) models and manipulated by a terminal computer, 3DP constructs parts in a very simple layer-wise manner rapidly. A typical process is as follows: A layer of powder is spread onto the powder bed on which the prototype is to be created. A print head, similar to that used in ink printing, is driven by an *X*–*Y* orientation system to eject binding materials onto the powder to produce the base layer according to the specified CAD pattern. The powder bed, driven by the piston rod in the *Z* vertical orientation, is then lowered by a predetermined layer thickness and the process is repeated until the required 3D shape has been produced. At the end of the process, unbound powder is removed, leaving the fabricated part[7,8].

3DP has unprecedented flexibility and outstanding manufacturing capability. It can exercise local control over the material composition, microstructure, and surface texture. The outstanding processing capabilities of 3DP have attracted more and more attention and have been utilized for rapid manufacturing in many areas. In the pharmaceutical field, 3DP can offer strategies and approaches for research and development of novel drug delivery systems (DDS) by being able to overcome some limitations of conventional formulation techniques in tailoring the microstructure of the tablets and the variations of composition in different regions of the tablets. Different types of novel DDS fabricated using 3DP have been reported[8–14], including zero-order controlled-release systems with content gradients of release-retardant polymers or concentration gradients of active ingredients in them, breaking-away tablets, drug delivery microchip, multiunit DDS, controlled-release pills, implantable DDS, and multiphase release dosage forms.

Tablets prepared from 3DP processes have some concrete advantages as oral fast disintegrating dosage forms: the low bulk density but high porosity of 3DP products in nature[11], the possible incorporation of loose powder in their inner parts, the non-compression consolidation mechanism, and, based on the reasonable selection of excipients, some, or even all, of the active ingredients may be present in an amorphous state in the FDTs. Here, we describe the design of FDTs with loose powder in their central regions to further increase the porosity and their preparation using 3DP. The resulting 3DP FDTs were subjected to pharmacotechnical analysis, mechanical performance tests, scanning electron microscopy, in vitro disintegration, and dissolution tests.

Experimental

Materials

Acetaminophen (APAP) was obtained from the 4th Pharmaceutical Factory of Weifang (Shandong, China). Methylene blue was purchased from J&K Chemica (Shanghai, China). Colloidal silicon dioxide, polyvinylpyrrolidone K30 (PVP K30), lactose, mannitol, and PVPP (crosslinked polyvinylpyrrolidone) were purchased from Shanghai Yunhong Pharmaceutical Aids and Technology Co., Ltd. (Shanghai, China). All other chemicals used were analytical grade, and water was distilled just before use.

Design

A schematic diagram of the FDT is shown in Figure 1. The FDT has three sections, the top and the bottom sections being compact, and the middle section is nonuniform with a compact peripheral region surrounding the center, which was filled with loose powder for fast disintegration.

Build sequence

The desktop 3DP machine was assembled at Shanghai Folichif Co. Ltd. (Shanghai, China) and consists of a powder delivery system, a platform, a powder dispensing system driven reciprocally along the length of the powder bed that has a size of 250 × 200 mm, and a printing system driven by the stepping motor assembled in a raster fashion with the switch on and off. The printing system has two custom-made drop-on-demand thermal print heads, each with four spray nozzles.

The process starts with depositing a layer of powder at the powder bed. In the powder dispersion system, which consists of a hopper and a rotary dispenser mounted horizontally at the bottom of the hopper, some amount of powder is dispensed at the front edge of the powder bed. Then the powder is distributed and compressed by the roller. Based on the CAD representations, the binder liquid is subsequently deposited by the print heads in a two-dimensional pattern onto the selected

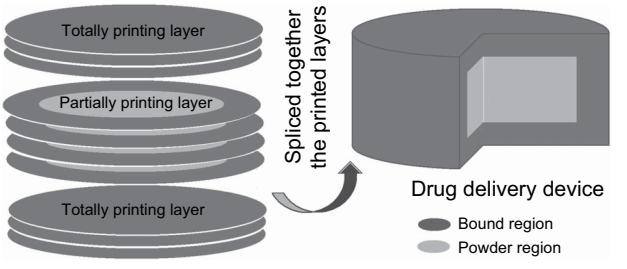

Figure 1. A schematic diagram of the FDT.

regions of the layered powder to form layers of the FDT. Once a layer is completed, the piston is moved downward in the chamber by the thickness of a layer, and the process is repeated for preparation of the next layer.

After completion of the tablets, the powder bed is elevated and extra powder is brushed away leaving the 'wet' tablets. The 'wet' tablets are allowed to dry at 35°C under vacuum (320 Pa) in a ZKF electric vacuum drying oven (Shanghai Laboratory Instrument Work Co. Ltd., Shanghai, China) to facilitate the removal of moisture and residual solvent. The drying tablets are left in the oven and excessive unbound powder is brushed away once again before analysis.

Preparation

For all the experiments, powder particle size was below 125 μm. Mixed powder is composed of APAP, lactose, PVP K30, mannitol, and colloidal silicon dioxide in the ratio of 40:20:9.5:30:0.5 by weight. The binder liquid was a solution of methylene blue (0.5%, w/v) and PVP K30 (5.0%, w/v) in 75% (v/v) of ethanol in water. Methylene blue was used as a color print marker to allow easy visualization.

Parameters were used as follows in preliminary experiments: 40 μm as the spacing of droplets within the direction of raster motion, 100 μm as the line-to-line spacing, 0.4×12 (nL × kHz) as the velocity of printing, and 1 minute as the interval time between two printing passes. Other prototyping parameters of the FDT are shown in Table 1. Sixteen millimeters was taken for the central distance among the FDTs. A batch of the fabrication could produce 15×12 FDTs (Figure 2).

Compressed tablets for comparison were prepared by the conventional direct compression procedure using a TDP-0 Single Punch Tablet Press (Shanghai Tianfan Pharmaceutical Machinery Factory, Shanghai, China) at a compression force of 20 kN with the same mixed powder. Additional 10% by weight of PVPP was mixed into the 3DP laying powders for direct compression.

Pharmacotechnical properties of the FDTs

The pharmacotechnical properties of FDT were determined as described below. The thickness and the diameter of six tablets were determined using a vernier caliper. Values are expressed in mm as mean ± SD. The

Table 1. Prototyping parameters.

Region	Layer no.	Layer thickness (μm)	Printing regions	Printing passes	Printing intervals (minutes)
Bottom	1–6	200	10 mm circle	3	3
Middle	7–18	200	2 mm peripheral ring	3	3
Top	19–24	200	10 mm circle	3	3

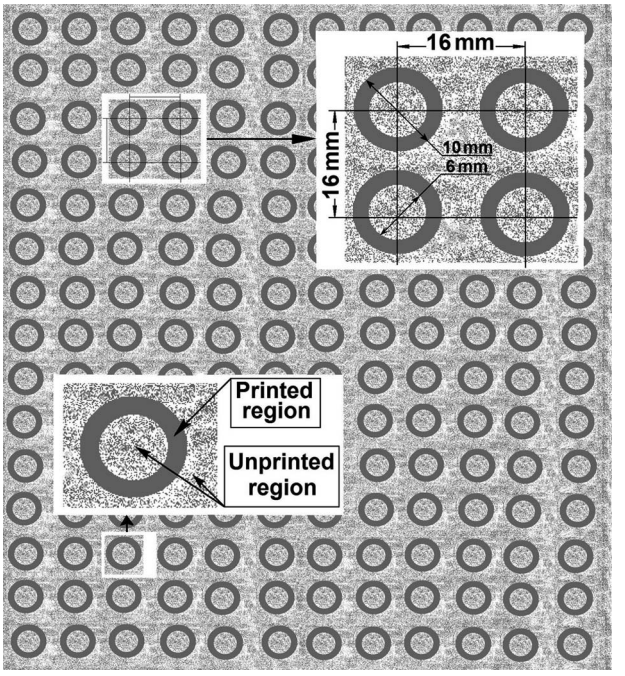

Figure 2. A CAD model for printing on the selected regions of a layered powder.

weights of 20 tablets were measured using an electronic balance (Sartorius, Göttingen, Germany). The mean value ± SD was expressed in milligrams.

To analyze drug content, 20 tablets were ground to powder using an agate mortar and pestle. Five grams of the ground powder was transferred into a 1000-mL volumetric flask and was dissolved with phosphate buffer solution (PBS, pH6.8) to prepare the samples for UV analysis. The solution was shaken for 60 minutes and then filtered through a 0.45-μm membrane filter (Millipore, Bedford, MA, USA). The resulting solution was diluted appropriately with PBS for UV analysis. Absorbance at 257 nm was used to measure the amount of APAP in the sample FDT.

A total of 12 FDTs from different batches were tested for content uniformity[15]. Each FDT was individually weighed and then was broken up and dissolved in PBS using 1000-mL volumetric flasks by shaking for 30 minutes. After filtration and dilution, the absorbance at 257 nm was taken and the amount of APAP in each FDT was calculated.

Mechanical performance of FDT

The mechanical performance of tablets (often evaluated by hardness and friability) is used as a parameter of quality control to ensure that the tablets prepared are reproducible and can withstand the subsequent handling procedures.

In this study, hardness of tablets is determined by crushing tests with a PYS-1 hardness tester (Shanghai

Huanghai Drug Control Instrument Co. Ltd., Shanghai, China). Ten FDTs were analyzed as a group. The measured hardness was expressed in terms of tensile strength, which was calculated by the following formula, according to Fell and Newton[16]:

$$\sigma = \frac{2P}{\pi Dt}, \quad (1)$$

where σ = tensile strength (kg/cm^2), D = tablet diameter (cm), t = tablet thickness (cm), and P = force applied to fracture (kg).

The friability of 20 FDTs was determined using a 285 mm diameter, 39 mm wide drum friabilator (FT-2000A; Tianjin University Radio Factory, Tianjin, China) at 25 rpm for 4 minutes. The tests were carried out in triplicate. The friability was expressed in terms of weight loss and was calculated as the percentage (% ±SD) of the initial weight according to the following equation:

$$f = \frac{W_0 - W_t}{W_0} \times 100\%, \quad (2)$$

where f = friability, W_0 = initial weight of 20 FDTs before the tests, and W_t = 20 FDTs weight after the tests.

Inner structural characteristics

A digital video camera (Canon, Tokyo, Japan) and an environmental scanning electron microscope (ESEM; FEI Corporation, Hillsboro, OR, USA) were employed to observe the FDT's inner structural characteristics. The FDT was sliced into two parts horizontally. The sample was mounted on a metal stub with a double-side adhesive tape for observation.

Wetting time and disintegrating time

The wetting time was measured by a modification of the described procedure by Rawas-Qalaji et al.[17] The FDT was placed at the center of two layers of absorbent paper fitted into a rounded plastic dish with a diameter of 12 cm. After the paper was thoroughly wetted with distilled water, excess water was completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet was then recorded.

The disintegration time was determined using a LD-2D disintegration test apparatus (Shanghai Huanghai Drug Control Instrument Co. Ltd.). Distilled water kept at 37°C was used as a medium and the basket was raised and lowered at a constant frequency of 30 cycles/min[18].

In vitro dissolution tests

In vitro dissolution studies were conducted by the paddle method using a USP 23/NF 18 Type II apparatus (Tianjin University Radio Factory) at 50 rpm in 900 mL of PBS at pH 6.8°C and 37°C. At predetermined time intervals, samples of 5.0 mL were withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant immediately by means of injectors. After filtration through a 0.45-μm membrane (Millipore) and appropriate dilution with PBS, the sample solutions were analyzed at 257 nm by a UV spectrophotometer (Unico Instrument Co. Ltd., Shanghai, China). The amount of APAP present in the sample was calculated with the help of an appropriate calibration curve constructed from reference standards. All the measurements were carried out six times and the mean value calculated.

Results and discussion

Pharmacotechnical properties of the FDTs

The mean diameter ± SD of six FDTs was 10.02 ± 0.04 mm. The mean thickness of six FDTs was 4.78 ± 0.06 mm. The mean weight of 20 FDTs was 314.8 ± 3.5 mg. The mean dose of the 12 FDTs was 128.6 ± 1.7 mg. The SD and the relative SD were 1.7 mg and 1.3%, respectively, exhibiting negligible content variation. All the results showed that the FDTs had acceptable pharmacotechnical properties.

Mechanical performance of FDTs

The tablets showed an acceptable hardness value of 54.5 ± 4.2 N/cm^2. The total mass loss during the friability test was 0.92 ± 0.14%.

In the FDTs of this study, the top and bottom layers were designed to be different from the middle layers allowing the FDTs having stronger top and bottom, thereby increasing hardness and reducing friability. A large part of the central region was filled with loose powders, which was beneficial for the fast disintegration of FDTs but impaired the mechanical properties of FDTs. Practically, the mechanical performance of FDTs could be manipulated not only by adjusting the dimensions of the central powder region but also by increasing the number of passes of printing binder solutions on the top and bottom layers, as well as the peripheral regions of the middle layers of FDTs.

One limitation of 3DP products is the mechanical properties, many 3DP products do not have enough hardness for post-treatment because of high porosity and poor binding effect among particles[7]. In this investigation,

the FDTs exhibited good mechanical performance. APAP is freely soluble in ethanol and could be bound together after reprecipitation. Thus partial dissolution of APAP particles in the printing process was beneficial for the tablets' mechanical performance.

In addition, two other types of binding mechanisms might be involved during the FDTs prototyping process[19], which deserve to be further investigated. First, the binder contained the dissolved adhesive PVP, which was left behind when the solvents of binder liquid evaporated. Second, the mixed powders contained particles of solid PVP, which were activated and acted as a binder upon absorption of water or ethanol. Thus different binding mechanisms combined together to give the FDTs enough mechanical strength.

Inner structure

The image recorded by the digital video camera is shown in Figure 3a. The printed regions exhibited a color of light blue because of the methylene blue separated out from the binder solution after its solvents evaporated, whereas the unprinted regions exhibited a color of white, the natural color of the mixed powder.

ESEM images of a FDT and its inner structures of different regions were shown as Figure 3b–d. It was clear by comparison that the peripheral region and the central region of the FDT were totally different. The peripheral annularity was well bound together. The particle size was reduced or individual particles could no longer be distinguished due to the printing of binder solutions. In contrast, the unprinted regions were uncompacted with cracks and fissures among the loose powders and the particles were almost in their original shapes. The high porosity of the unprinted regions was certainly beneficial for the penetration of solvent molecules and thus the disintegrating of the FDTs.

Figure 3b and c shows that the boundaries between the printed and unprinted regions are not very distinct, reflecting the migration of solvents in the printing solutions, that is, water and ethanol. The migration of the solvents and the existing of highly hygroscopic PVP particles in the mixed powders together caused the weak bridge-like binding effects among the particles in the unprinted regions (Figure 3e).

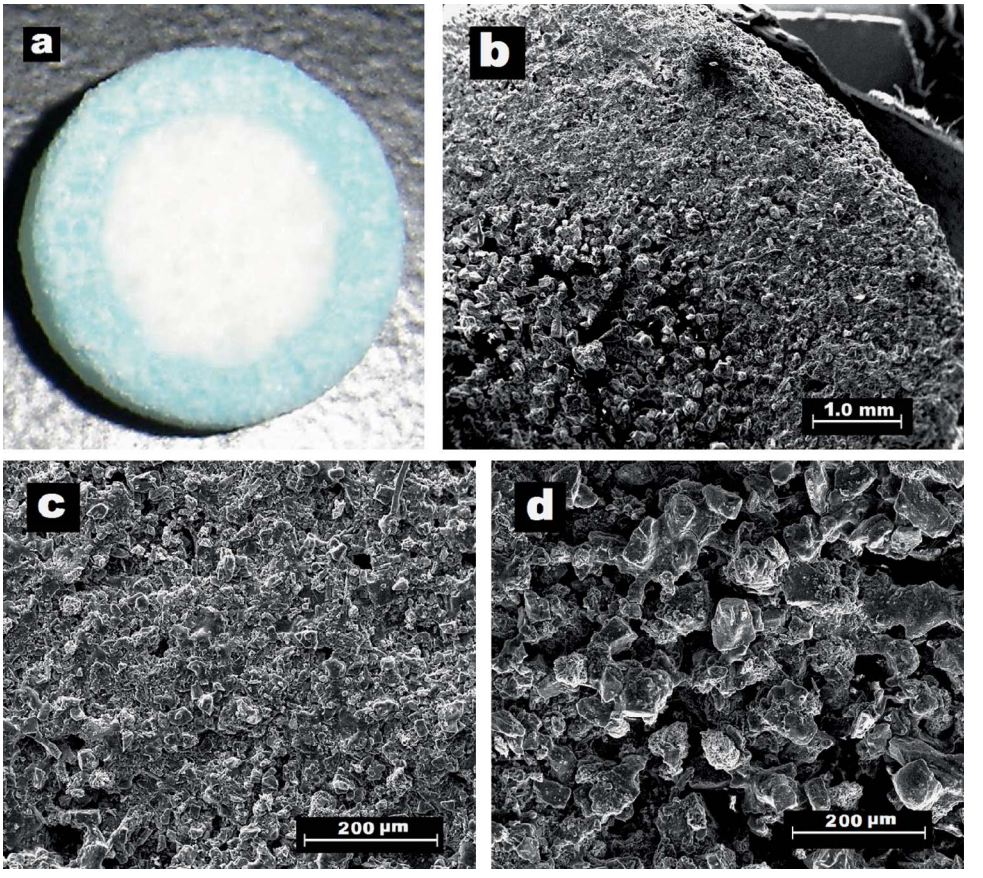

Figure 3. ESEM images and photo of inner structure of the FDT. (a) Optical image of the horizontal cross section, (b) ESEM image of a quarter of the cross section, (c) ESEM image of the peripheral bound region, and (d) ESEM image of the central powder region.

Wetting time and disintegrating time

The average disintegration time of six FDTs was 21.8 ± 5.4 seconds. The average wetting time of six FDTs was 51.7 ± 7.5 seconds. All the tested FDTs exhibited acceptable wetting time and rapid disintegration, well within 2 minutes, specified as the acceptable time limit for FDTs in the USP.

The rapid dissolving or disintegrating properties of FDTs have a close relationship with the wetting characteristics of the excipients in the tablets. The usage of PVP both as one ingredient of the mixed powders and as binder in the printing solutions was not only beneficial for the prototyping of FDTs but also for the fast wetting and disintegration of FDTs because of its highly wettability and water absorbability.

On the other hand, the degree of FDTs' porosity played an important role in tablet wetting and disintegration. The pores form capillary pathways that allow rapid water penetration throughout the FDTs. The high porosity of the FDTs in this research derived from the special laminated-fabrication manner of the 3DP process designed to promote the rapid wetting and disintegration of FDTs.

In 3DP processes, the consolidation behavior of the materials and drugs are totally different from that of the traditional direct-compressed method or the granulation methods. Thus the existing state of drugs or materials before and after 3DP process, the possible interactions between the drugs and the excipients in the dissolution and reprecipitation processes will be thoroughly investigated for further development of novel DDS.

In vitro dissolution tests

The results of in vitro dissolution tests are shown in Figure 4. About 97.7% of the drug was released in the initial 2 minutes for FDTs. Although almost the same percentage of APAP was free into the dissolution medium in the first minute for the compressed FDTs, only 87.1% of the APAP was detected at the second minute, and the time for APAP to completely release was 15 minutes. An unfavorable prolonged tailing-off of release toward completion was resulted from the big APAP particles and their uneven distribution in the compressed FDTs[19,20]. 3DP FDTs were able to completely avoid the tailing-off of drug release. It can be suspected that the advantage of 3DP FDTs is more obvious if the aqueous solubility of an incorporated active ingredient is smaller than that of APAP.

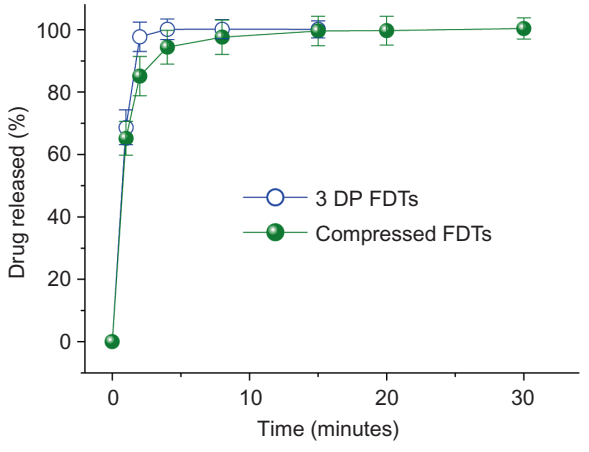

Figure 4. Accumulative drug release profiles.

Besides fast disintegration of FDTs, another reason for the fast dissolution and release of APAP was that partial dissolution of APAP particles during the printing processes had greatly diminished the particles' dimensions in the printed regions, which was able to improve APAP's dispersibility in the FDTs to some extent and maybe change the physical status of some APAP from crystals to amorphous state.

Polymer science is the backbone for the development of new DDS for the past few decades and tremendous efforts have concentrated on synthesis of new polymers and modifying the chemical and physical properties of the existing synthetic or natural polymers[21]. On the contrary, considerably less effort has been spent on the processing control of three-dimensional position, microstructure, and composition variations during the manufacturing process. This lack of interest may be related to the fact that no existing techniques offer control of these parameters accurately and reproducibly, and DDS with simple structure design features often add extra processing steps and variability to manufacturing when conventional pharmaceutical technologies are employed[8,22]. Novel strategies provided by the advanced technologies for the development of pharmaceutical products deserve to be paid more attention.

On the other hand, the consolidation behaviors of the mixed powders in 3DP processes were totally different from those of the traditional direct-compression method or the granulation methods, which result in different fast disintegrating mechanisms. For traditional FDTs, they often rely exclusively on the fast swelling of the disintegrants or gas generation of effervescent couples to achieve enough disintegrating force for fast disintegration when the direct compression method is employed[23].

In contrast, the 3DP FDTs can achieve fast disintegrating property from the following four aspects: the high porosity nature of 3DP products, the incorporation of loose powder in their inner parts, the possible amorphous physical status of drug, and the usage of hydrophilic polymer PVP as adhesives. After rapid absorbance of the dissolution medium, PVP in the peripheral bound region dissolved quickly and resulted in fast disintegration of the 3DP FDTs.

Conclusions

A novel FDT with loose powders for achieving fast dissolving properties was designed and fabricated using a simple and repeated 3DP process. The FDTs showed acceptable pharmacotechnical properties and exhibited standard-met mechanical performance with a hardness value of 54.5 ± 4.2 N/cm^2 and 0.92 ± 0.14% total mass loss during the friability tests because of the synergistic action of different binding mechanisms. ESEM images clearly showed that the printed regions were bound together. The particle size was reduced or individual particles could no longer be distinguished. In contrast, the unprinted regions were uncompacted with cracks and fissures among the loose powders. All the FDTs could disintegrate and wet rapidly in the in vitro tests. The average disintegration time of FDTs was 21.8 ± 5.4 seconds and the average wetting time was 51.7 ± 7.5 seconds. The in vitro dissolution tests demonstrated that 97.7% of the drug was released in the initial 2 minutes. 3DP process is able to offer novel methods for preparing FDTs.

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