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Research Paper

Novel oral fast-disintegrating drug delivery devices with predefined inner structure fabricated by Three-Dimensional Printing

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Abstract

Objectives Novel fast-disintegrating drug delivery devices with special inner structure characteristics were designed and fabricated using Three-Dimensional Printing.

Methods Based on computer-aided design models, fast-disintegrating drug delivery devices containing loose powders were prepared automatically using the Three-Dimensional Printing system. The inner powder regions were prepared by depositing the binder solutions onto selected regions during the layer-printing process.

Results The devices showed acceptable pharmacotechnical properties and fine hardness (63.4 N/cm^2) due to the synergistic action of several binding mechanisms, but unsatisfactory friability, with 3.55% total mass loss during the friability tests. Scanning electron microscope images clearly showed that the printed regions were well bound, and that the drug 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 mixed powder. All the drug delivery devices disintegrated and wetted rapidly in in-vitro tests. The average disintegration and wetting times were 23.4 s and 67.6 s, respectively. Dissolution tests showed that 98.5% of the drug was released within 2 min.

Conclusions Three-Dimensional Printing offers strategies for the development of novel oral fast-disintegrating drug delivery devices.

Keywords binding mechanisms; fast-disintegrating drug delivery devices; inner structure; mechanical performance; Three-Dimensional Printing

Introduction

Fast-disintegrating/dissolving tablets (FDTs) have been in ever-increasing demand over the last decade because of their advantages such as good stability, accurate dosing, convenience for patients, easy administration and no risk of choking. The popularity and usefulness of the formulation has resulted in the development of several technologies based on lyophilisation, moulding, sublimation, compaction, spray drying, moisture treatment and sintering for the development of FDTs with standard mechanical and pharmacotechnical properties.[1–3]

Key properties of FDTs relate to fast wetting and absorption of water into the tablets and the disintegration of associated particles into individual components for fast dissolution. To achieve this, the tablet structure must have a highly porous network. 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 technologies and novel strategies to increase tablet porosity without sacrificing mechanical performance are therefore desired.[1,4]

Three-Dimensional Printing (3DP) is an advanced rapid prototyping technology which takes virtual designs from computer-aided design or animation modelling software,

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transforms them into thin, virtual, horizontal cross-sections and then creates each cross-section in physical space, one after the next, until the model is finished. A typical 3DP process is shown in Figure 1. Because of its easy, flexible and highly reproducible manufacturing process, 3DP has some advantages over conventional compression technologies for the fabrication of solid dosage forms, and can provide novel strategies for the design, development, manufacturing and commercialisation of many types of solid dosage forms. The 3DP process has been used to fabricate drug delivery devices that offer linear release profiles, colon-targeted drug release, time-controlled release and multi-phase release.[5–11]

The 3DP processes has some concrete advantages for preparing oral fast-disintegrating drug delivery devices (FD-DDDs): the high porosity of 3DP products,[9] 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 FD-DDDs. After dissolution of the binder among particles formed during the 3DP process, the drug delivery devices disintegrate quickly.

In the present study, a novel FD-DDD with predefined inner structural characteristics for fast dissolution was designed, and a simple and consistent 3DP process was developed. The resulting FD-DDDs were evaluated using pharmacotechnical property tests, mechanical analysis, scanning electron microscopy and in-vitro disintegration and dissolution tests.

Materials and Methods

Materials

Paracetamol (acetaminophen) was obtained from the 4th Pharmaceutical Factory of Weifang (Shandong, China). Alizarin yellow was purchased from J&K Chemica (Shanghai, China). Colloidal silicon dioxide, polyvinylpyrrolidone K30 (PVP K30), lactose and mannitol were purchased from Shanghai Yunhong Pharmaceutical Aids and Technology Co. Ltd. (Shanghai, China). All other chemicals were analytical grade. Water was distilled just before use.

Design

A schematic diagram of the FD-DDD is shown in Figure 2. This FD-DDD comprises three sections: the top and bottom sections are compact and uniform, while the middle section is non-uniform, containing loose powders for fast dissolution, and with a 'bound plus' for improving the hardness of the FD-DDD.

Within a layer of the FD-DDD, the 3DP print heads dispense binder liquid onto the whole circular area to form a totally printed layer during the printing passes. (A 'printing pass' means the print heads pass once over the powder bed for printing.) Several totally printed layers are bound together to form the top and bottom compact sections. In the middle section, the binder liquid is printed during the printing passes only onto partially selected regions, based on the computer-assisted design model, to form a partially printed layer. After accumulation of a number of partially printed layers, a peripheral bound cirque and a central bound plus are fabricated automatically with loose unbound powders between them.

Construction

The desktop 3DP machine was assembled at Shanghai Folichif Co. Ltd (Shangai, China). The machine consists of

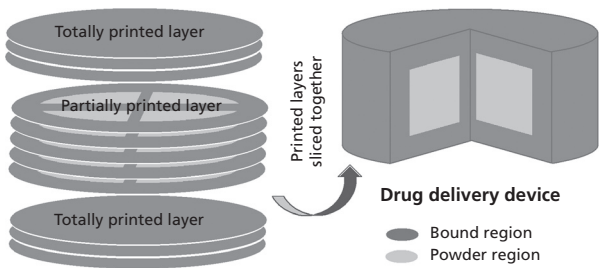

Figure 2 Structure of the fast-dissolving drug delivery device.

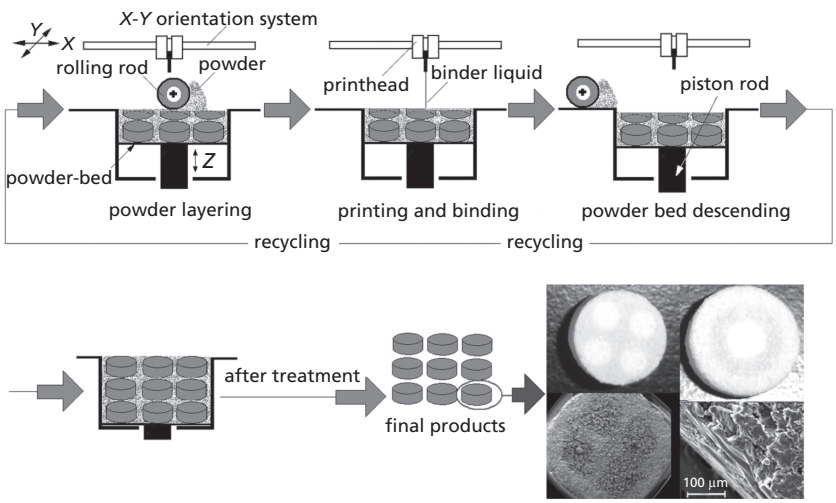

Figure 1 The Three-Dimensional Printing process.[5]

a powder delivery system, a platform, a powder dispensing system, driven reciprocally along the length of the powder bed, which 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 having four spray nozzles.

The process begins by depositing a layer of powder on the powder bed. In the powder dispersion system some powder is dispensed at the front edge of the powder bed, which consists of a hopper and a rotary dispenser mounted horizontally at the bottom of the hopper. The powder was then distributed and compressed by the roller. Based on the computer-aided design representations, the binder liquid was subsequently deposited by the print heads in a two-dimensional pattern onto the selected regions of the layered powder and formed the layers of the FD-DDDs. Once the layer was complete, the piston was moved downwards in the chamber by the thickness of a layer, and the process was repeated for the preparation of the next stratum (Figure 1).

After completion of the FD-DDDs, the powder bed was elevated and extra powder brushed away, leaving the 'wet' FD-DDDs. These were allowed to dry for several days 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 ethanol.

Preparation

Different powders were separately sieved manually through a 125 μm mesh sieve. Mixed powder composed of paracetamol, lactose, PVP K30, mannitol and colloidal silicon dioxide, in the ratio 40 : 20 : 9.5 : 30 : 0.5 by weight, was prepared using a powder mixer (Shanghai TianFeng Pharmaceutical Equipment Co., Ltd, Shanghai, China). The binder liquid was a solution of alizarin yellow (0.5% w/v) and PVP K30 (5.0% w/v) in 75% (v/v) ethanol in water. Alizarin yellow was used as a colour print marker to allow easy visualisation.

The following parameters were used 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 min as the interval between two printing passes. Other prototype parameters of the FD-DDDs are shown in Table 1. The central distance among the FD-DDDs was set as 16 mm. A batch of the fabrication could produce a 15 × 12 array of FD-DDDs (Figure 3).

Compressed tablets for comparison were prepared using the same mixed powders 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.

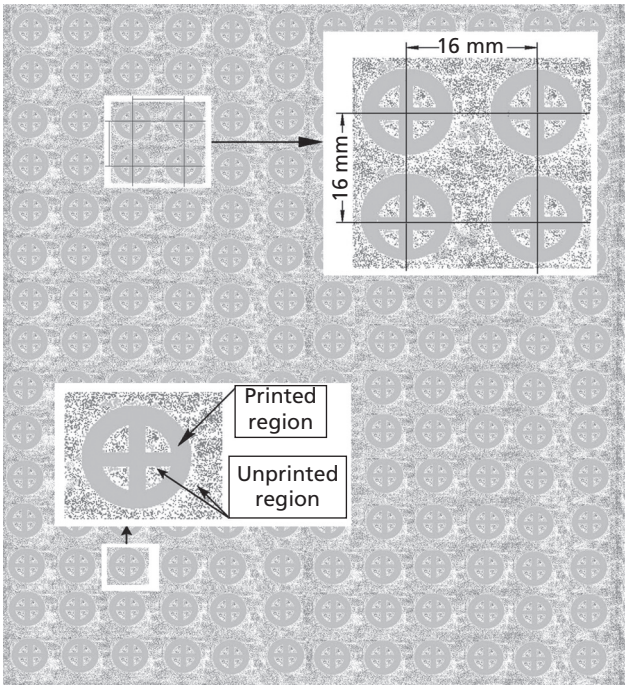

Figure 3 A computer-assisted design model for printing on the selected regions of a layered powder.

Pharmacotechnical properties of the FD-DDDs

The thickness and the diameter of the tablets were determined using Vernier callipers. Values are expressed in mm, as mean ± SD of six tablets. The weight of the FD-DDDs was measured using an electronic balance (Sartorius, Göettingen, Germany) and is given in mg, as mean ± SD of 20 tablets.

To analyse drug content, 20 FD-DDDs were ground to powder using an agate mortar and pestle and 5 g of the ground powder was transferred into a 1 litre volumetric flask and dissolved in phosphate buffer solution (pH 6.8) to prepare the samples for UV analysis. The solution was shaken for 60 min and then filtered through a 0.45 μm membrane filter (Millipore, Bedford, MA, US). The resulting solution was appropriately diluted with the same solvent for UV analysis.

Twelve FD-DDDs from different batches were tested for content uniformity. Each FD-DDD was weighed individually then broken up and dissolved in phosphate buffer solution

Table 1 Prototyping parameters for preparing all layers of the fast-dissolving drug delivery device

Region	Layer no.	Layer thickness (μm)	Printing regions	Printing passes[a]	Printing interval (min)
Bottom	1–6	200	10 mm circle	2	2
Middle	7–18	200	Partially selected	2	2
Top	19–24	200	10 mm circle	2	2

[a]Number of times that the print heads pass over the powder bed for printing.

in a 1 litre volumetric flask by shaking for 30 min. After filtration and dilution, the absorbance at 257 nm was measured using a UV spectrophotometer (Unico Instrument Co. Ltd, Shanghai, China). The amount of paracetamol present in the sample was calculated from a calibration curve constructed as per the Chinese Pharmacopeia (2005 ED).[12]

Mechanical performance of FD-DDDs

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

In this study, hardness of tablets was determined by crushing with a PYS-1 hardness tester (Shanghai Huanghai Drug Control Instrument Co. Ltd, Shanghai, China), Ten FD-DDDs were analysed as a group, and the measured hardness was expressed in terms of tensile strength, which was calculated from the formula: $\sigma = 2P/\pi Dt$ where σ is tensile strength (kg/cm^2), D is the tablet diameter (cm), t is the tablet thickness (cm), and P is the force applied to fracture (kg).[13]

The friability of 20 FD-DDDs 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 min. Tests were carried out in triplicate and the friability, expressed in terms of weight loss, was calculated as the percentage of the initial weight according to the following equation: $f = (W_0 - W_t)/W_0$ where f is friability, W_0 is the initial weight of the 20 DDDs before the tests and W_t is their weight after the tests.

Inner structural characteristics

A digital video camera (Canon, Tokyo, Japan) and an environmental scanning electron microscope (FEI Corporation, Hillsboro, OR, US) were used to observe the inner structural characteristics of the FD-DDDs. FD-DDD samples were sliced horizontally into two parts. The sample was then mounted on a metal stub with double-sided adhesive tape and coated under vacuum with gold in an argon atmosphere prior to scanning.

Wetting time

The wetting time was measured using a modification of the procedure reported by Rawas-Qalaji *et al.*[14] An FD-DDD was placed between two layers of absorbent paper fitted into a round plastic dish (diameter 12 cm). After wetting the paper with water, excess fluid was drained and the time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet was recorded using a chronometer. The experiments were repeated six times.

Disintegration time

The disintegration time was determined using an LD-2D disintegration test apparatus (Shanghai Huanghai Drug Control Instrument Co. Ltd, Shanghai, China). Water at 37°C was used as the medium and the basket was raised and lowered at a constant frequency of 30 cycles/min.[15] The experiments were repeated six times.

In-vitro dissolution tests

In-vitro dissolution studies were conducted according to the Chinese Pharmacopoeia (2005)[12] method II paddle method using an RCZ-8A dissolution apparatus (Tianjin University Radio Factory) at 100 rpm in 900 ml phosphate buffer solution (pH 6.8, 0.1 M) at 37°C. At predetermined time intervals, samples of 5.0 ml were withdrawn from the dissolution medium by means of injectors and immediately replaced with fresh medium to keep the volume constant. After filtration through a 0.45 μm membrane (Millipore) and appropriate dilution with phosphate buffer solution, the paracetamol concentration in the sample solutions was determined as described above. Measurements were carried out six times and the mean calculated.

Statistical methods

The cumulative percentage of paracetamol released from the compressed tablets and the FD-DDDs *in vitro* ($n = 6$) at 1, 2 and 4 min was analysed by analysis of variance (ANOVA). The difference was considered significant when the P value was less than 0.05.

Results

Pharmacotechnical properties of the FD-DDDs

The diameter of the FD-DDDs was 9.98 ± 0.04 mm and the thickness was 4.77 ± 0.06 mm (mean ± SD, $n = 6$). The mean weight was 326.5 ± 4.2 mg ($n = 20$). The mean content was 131.5 ± 2.2 mg ($n = 12$). The SD and relative SD were 2.2 mg and 1.7%, respectively, exhibiting negligible content variation. All the results showed that the FD-DDDs had acceptable pharmacotechnical properties.

Mechanical performance of FD-DDDs

The tablets showed an acceptable hardness value of 63.4 ± 5.4 N/cm^2 but an unsatisfactory friability: the total mass loss during the friability test was 3.55 ± 1.16%.

Inner structure

The image recorded by the digital video camera is shown as Figure 4a. The printed region was characterised by the yellow chromatogen, alizarin yellow, as this separated from the binder solution after solvent evaporation; the unprinted region was colourless.

Scanning electron microscope images of the inner structures of different regions in the FD-DDDs are shown in Figure 4b–d. PVP is an amorphous polymer and its particles do not have a regular shape,[16] whereas paracetamol is always present as large prismatic white crystals.[17]

Wetting time and disintegration time

The average disintegration time of the FD-DDDs was 23.4 ± 6.1 s. The average wetting time was 67.6 ± 6.3 s (both $n = 6$).

In-vitro dissolution tests

ANOVA showed significant differences ($P < 0.05$) in the cumulative percentage of drug released from the compressed tablets and the 3DP FD-DDDs at 1, 2 and 4 min. Up to 98.5%

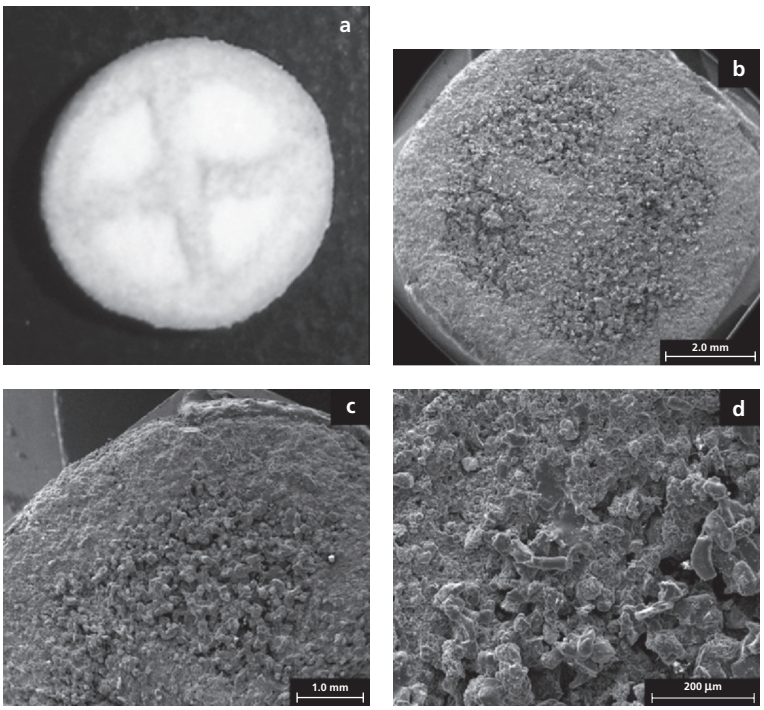

Figure 4 (a), Optical image of the cross-section of the fast-disintegrating drug delivery device. (b–d), Scanning electron microscope images at different magnifications.

of the paracetamol was released in the initial 2 min for FD-DDDs, whereas over 20 min was required for 98.7% of the compressed tablets to be released (Figure 5). The 3DP FD-DDDs exhibited both rapid disintegration and fast release of the active ingredients.

Discussion

The the results of the tests showed that the FD-DDDs had acceptable pharmacotechnical properties. The tablets showed an acceptable hardness value of 63.4 ± 5.4 N/cm^2 but an unsatisfactory friability: the total mass loss during the friability test was 3.55 ± 1.16%.

One limitation of 3DP products is the mechanical properties: many 3DP products do not have adequate hardness because of high porosity and poor binding of particles.[5] The acceptable hardness of the FD-DDDs we developed here may have resulted from the following aspects. First, PVP was used in the mixed powder. The particles of PVP in solid form could be activated through absorption of water or ethanol during the 3DP process and then act as a solid binder after drying of the FD-DDDs. Second, the binder liquid contained PVP, which would remain after the solvent has evaporated. PVP compounds always act as binders in traditional pharmaceutical preparations. Their adhesive and binding capacities are particularly important in tableting (wet granulation, dry granulation, direct compression and effervescent tablets), in film coatings and adhesive gels.[18] This study demonstrated that PVP could also exert important binding effects in 3DP products. Third, paracetamol is freely soluble in ethanol and could be bound together through a

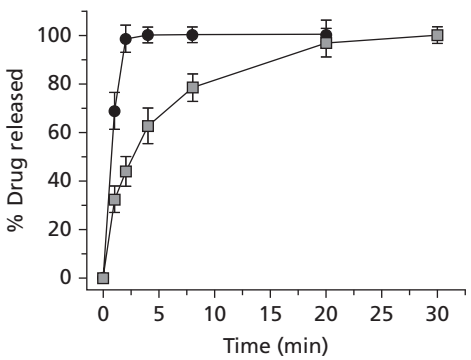

Figure 5 Cumulative drug release profiles of compressed tablets (■) and the fast-dissolving drug delivery devices (●).

dissolution–reprecipitation binding mechanism.[19] Partial dissolution of paracetamol particles in the printing process was beneficial for the hardness of the FD-DDDs, especially with the co-existence of PVP. Thus, in the prototyping of FD-DDDs, different binding mechanisms could act synergistically to provide products with sufficient mechanical strength. However, the total mass loss was poor and needs to be improved, according to the relevant guidelines.[12] This may be because solvent migration of the binder liquid during the printing process resulted in clinging of powders on the surface of FD-DDDs from their surrounding regions, which could not easily be brushed away.

Scanning electron microscope images of the inner structures of different regions in the FD-DDDs are shown in Figure 4b–d. It is clear from these images that the printed

regions were bound together through a dissolution–reprecipitation mechanism, and the drug particle size was reduced, or individual particles could no longer be distinguished. In contrast, the drug particles in the unprinted regions maintained their original shapes, displaying cracks and fissures (Figure 4d). The high porosity of the unprinted regions was beneficial for the penetration of solvent molecules and the fast disintegration of the FD-DDDs.

From Figures 4c and 4d it is clear that the boundaries between the printed regions and the unprinted regions were no longer distinct, and that particles in the unprinted regions have some connective properties. This potentially could be due to the migration and bleeding of binder liquid solvents, and the presence of PVP, which is both highly water and ethanol soluble.

All the tested FD-DDDs exhibited acceptable wetting time and initial rapid disintegration, for which 2 minutes is specified as an acceptable limit for fast disintegrating tablets in the US Pharmacopeia.[20] The rapid wetting and disintegrating properties of FD-DDDs have a close relationship with the wetting characteristics of the excipients in them. The use of PVP as both an ingredient of the mixed powders and a binder in the printing solutions was beneficial not only for the prototyping of FD-DDDs but also for the fast wetting and disintegration of FD-DDDs, because of its highly solubility in water. On the other hand, the porosity of FD-DDDs played an important role in tablet wetting and disintegration. The pores form capillary pathways that allow rapid water penetration throughout the FD-DDDs. The enhanced porosity of the FD-DDDs in this study was derived from the special laminated production process of 3DP and this influenced their rapid wetting and disintegration.

Besides rapid disintegration of FD-DDDs, another reason for the fast dissolution and release of paracetamol was that partial dissolution of paracetamol particles during the printing processes had obviously diminished the particles' dimensions in the printed regions, which improved the dispersibility of paracetamol in the FD-DDDs to some extent and may change the physical status of some paracetamol molecules.

The 3DP process used in the present study is somewhat similar to the solvent methods for preparing solid dispersions. PVP compounds are excellent auxiliaries for the manufacture of effective solid solutions and dispersions by the solvent methods, because of their good solubility in water and a wide variety of organic solvents, rapid water uptake and their ability to inhibit crystallisation of dispersed drugs.[16,18] Thus, it was expected that paracetamol in the bound regions of FD-DDDs would be partially transferred to an amorphous state from crystalline particles in the presence of PVP, which would be useful for the fast dissolution of paracetamol; this will be investigated further.

Conventional FDTs have often relied exclusively on the physical and chemical characteristics of the disintegrants or effervescent couples to achieve fast disintegrating properties when the direct compression method is used. 3DP is extremely useful in the manufacture of FDTs because complex design characteristics can be reproduced in a simple and repetitive process. This research has demonstrated that 3DP can offer novel strategies for the preparation of FDTs. Certainly, 3DP can be used to create other novel DDDs with desired release profiles, achieved through tailoring the inner microstructure of the DDDs and surface texture and variations in the local functional materials and active ingredients.

Conclusions

A novel FD-DDD containing loose powders for fast disintegration was designed and fabricated using the 3DP process. The FD-DDDs showed acceptable pharmacotechnical properties and fine hardness because of the synergistic action of several binding mechanisms, but unsatisfactory friability. Scanning electron microscope images clearly showed that the printed regions were firmly bound, with no freely standing particles having diminished or disappeared, whereas the unprinted regions displayed cracks and fissures among the loose mixed powders. All the FD-DDDs disintegrated and were wetted rapidly in the in-vitro assays and showed almost complete drug release. Thus, 3DP is capable of offering new strategies for the development of novel FDTs.

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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