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Novel drug delivery devices for providing linear release profiles fabricated by 3DP

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ABSTRACT

Novel doughnut-shaped multi-layered drug delivery devices (DDDs) were developed with local variations of the drug and release-retardant material for providing linear release profiles. Based on computer-aided design models, different DDDs containing acetaminophen as a model drug, hydroxypropyl methylcellulose as matrix and ethyl cellulose (EC) as a release-retardant material were prepared automatically using a three-dimensional printing (3DP) system. *In vitro* dissolution assays demonstrated that all the 3DP DDDs had with different diameters, heights, concentrations of EC and central hole diameters were able to give linear release profiles. Morphological and erosion studies showed that acetaminophen was released through a simultaneous surface erosion process involving the outer peripheries and inner apertures. The barrier layers on both bases of DDDs had good adhesion strength with the drug-contained regions and offered consistent release retardation for the whole duration of the dissolution process. The release time periods of the DDDs were dependent on the annular thicknesses or the passes of binder solution containing a release-retardant material. The dosage of the DDD can be adjusted independently by changing the heights of the DDDs. Thus, 3DP is capable of offering novel strategies for developing DDDs with complex design features for desired drug release profiles.

1. Introduction

For conventional pharmaceutical tablets, there are two main approaches for providing constant drug release profiles. One method is to rely on the chemical and physical properties of the excipients; the other is to endow the tablets with special geometries or structural characteristics such as coating, multi-layering or utilizing the osmotic pump structure. Over the past several decades, different types of the tablet's geometry have been developed and have been reported as approaches to obtain zero-order drug release profiles. Examples include doughnut-shape (Sundy and Danckwerts, 2004; Kim, 1995, 1999; Cheng et al., 1999; Cleave, 1965), rectanglar (Dinesh and Samuel, 1990), biconvex (Narasimhan and Langer, 1997), parabolic (Mohsen, 1994), and core-in-cup format (Danckwerts et al., 1998). Among those, the doughnut-shaped tablets containing one or more cylindrical holes to provide a constant surface area for drug release have attracted most attention.

Early research demonstrated a rectangular tablet with holes and a mathematical model was proposed that stated a tablet with a central hole(s) would provide a constant drug release surface area (Cleave, 1965). Based on this study, more recent work has produced a flat uncoated doughnut-shaped tablet with a single central hole of various sizes for poorly soluble drugs (Kim, 1995). The hole was bored into the tablet by high-speed drilling. Later, this method was used to prepare a coated doughnut-shaped tablet for water-soluble drugs (Kim, 1999). About the same time, a similar uncoated doughnut-shaped tablet, whose central hole was bore drilled, was reported (Cheng et al., 1999). Although linear drug release profiles were exhibited, the production of doughnut-shaped tablets using conventional methods was deemed to be impractical from an industrial standpoint, as it was complex, time-consuming and required a discontinuous manufacturing process. More recently, a specially designed punch set for the production of donut-shaped tablets has been developed (Sundy and Danckwerts, 2004). The system still requires complicated procedures and lacks flexibility for practical purposes. Thus, simple and convenient processes are desired for producing tablets with intricate and complex design features.

Three-dimensional printing (3DP), an advanced rapid prototyping technique, was first developed at the Massachusetts Institute of Technology (Sachs et al., 1992). It has many advantages in preparing various types of solid drug delivery devices (DDDs). This is by virtue of its recognized capability and flexibility. Implantable DDDs prepared using 3DP were initially demonstrated (Wu et al., 1996; Yu et al., 2008). Later, the manufacture of oral DDDs using standard phar-

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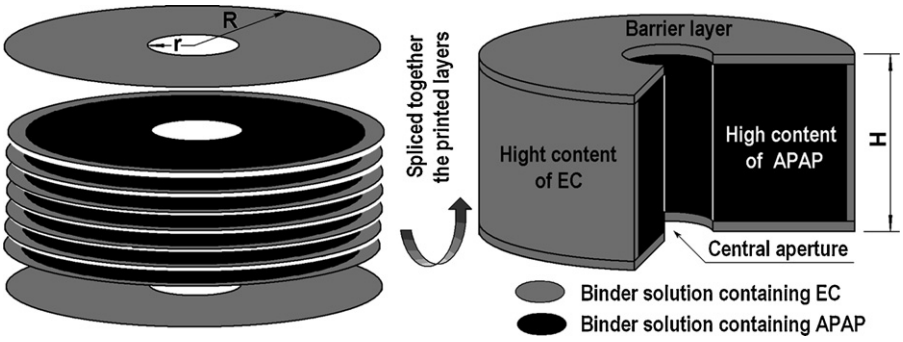

Fig. 1. A schematic diagram of the novel DDD.

maceutical materials and active matters were examined (Katstra et al., 2000; Rowe et al., 2000). More recently, DDDs with a gradient distribution of release-retardant materials and implants with a predefined microstructure have been reported (Yu et al., 2007; Huang et al., 2007). All these studies demonstrated that 3DP was capable of overcoming limitations that are apparent in traditional tablet manufacturing processes.

The present study demonstrates that doughnut-shaped, multi-layered structure and variations of local material and drug concentrations could be combined into a single DDD that provides linear release profiles *via* a simple and repeated 3DP process. Moreover, the release profiles of the DDDs and the dosage can be regulated independently by altering prototyping parameters.

2. Materials and methods

2.1. Materials

Acetaminophen (APAP) was obtained from the 4th Pharmaceutical Factory of Weifang (Shandong, China). Hydroxypropyl methylcellulose E100 (HPMC, Methocel E50 premium) was purchased from Shin-Etsu Chemical Co. Ltd. (Tokyo, Japan). Ethyl cellulose (EC, nominal viscosity: between 4.0 and 6.0 mPa s) was from Shandong Ruitai Chemical Co. Ltd. (Shandong, China). Polyvinylpyrrolidone K30 (PVP K30) and colloidal silicon dioxide were purchased from Shanghai Yunhong Pharmaceutical Aids and Technology Co. Ltd. (Shanghai, China). All other chemicals used were of analytical grade, and water was distilled just before use.

2.2. Design and preparation

2.2.1. Design concept

Design of a controlled drug release tablet is an integral part of pharmaceutical research and development (Zhang, 1999). The DDD consist of three sections, the top and bottom barrier layers and the drug-loaded section (Fig. 1).

The drug-free top and the bottom layers of the doughnut structure represent an inert and impermeable obstacle to water penetration and drug diffusion. This shifts the typical whole dimensional release towards release only from the outer and inner apertures' cylindrical surface of DDDs. As the outwardly releasing surface area decreases with time, the inwardly releasing area increases synchronously in the dissolution process. Hence, the erodible surface area of the DDDs in a unit time remains stable if the poor water-soluble drugs are released solely by hydrophilic polymer erosion mechanism (Kim, 1999; Karasulu et al., 2000).

It is well established that although a constant release surface area may be maintained during the dissolution processes, the drug release rates are initially faster than those in the later stage of the process. This is due to the existing drug particles on the surface of the DDDs; absorbing of water and gelling of HPMC that occurs after the DDDs are placed into the dissolution medium. To eliminate this phenomenon, the drug-contained section is divided into two regions. The peripheral annulus region with a thickness of 200 μm has a high content of release-retardant materials, while the inner annulus region has a high content of the drug. The erosion of the DDD surface is reduced and slower at the beginning of dissolution than later. Combined with the relatively lower concentration of drug in the peripheral annulus region, the initial faster release rates can be counterbalanced to provide a linear release profiles during the whole release period.

Thus, the doughnut macro-shape, multi-layered structure and ingredient variations are combined together in a single DDD for providing linear drug release profiles.

2.2.2. Build sequence

The 3DP machine was assembled by Fochif Mechatronics Technology Co. Ltd. (Shanghai, China). The 3DP process began by depositing a layer of powder at the powder bed with a size of 250 mm × 200 mm. The binder solutions were deposited by print heads in a two-dimensional pattern onto the layered powder and formed a layer of the DDDs. Once a layer had been completed, the piston was moved downward by the thickness of a layer, and the process was repeated for the next layer. More details have been described previously (Huang et al., 2007; Yu et al., 2007).

Printing instructions for each layer were derived directly from a CAD representation containing the similar DDDs' models. The bottom and the top barrier layers of the DDDs were formed by depositing droplets of binder I [binder solutions containing 2.0% (w/v) of EC in 90% (v/v) of ethanol in water] onto the manually spread EC powder in the selected areas for three passes.

The drug-contained regions were prepared as follows: (1) a layer of powders containing APAP were automatically spread out; (2) powders of the outer 0.2 mm annular regions were bound together by dispensing binder I for one pass; (3) binder II [binder containing 10.0% (w/v) of APAP in (v/v) 90% ethanol in water] was deposited onto powders of the inner regions for one pass to complete one layer of the DDDs. During printing, the powders in the DDDs central regions were not deposited with any of the binder solutions. To minimize bleeding of the binder solutions due to over-saturation, an interval time was allowed for earlier-deposited liquid to be at least partially dried before the next pass.

After completion of the tablets, the powder bed was elevated and residual powder was brushed away leaving the "wet" tablets. The "wet" tablets were allowed to dry overnight at 35 °C under vacuum (320 Pa) in a ZKF Electric Vacuum Drying Oven (Shanghai Laboratory Instrument Work Co. Ltd., Shanghai, China). Excess unbound powder was again brushed away.

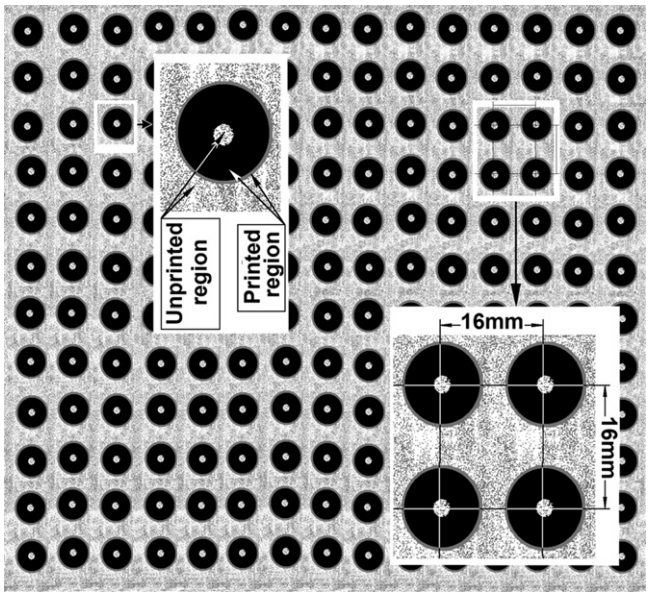

Fig. 2. A CAD model for printing on the selected regions of a layered powder.

2.2.3. Preparation

For all the experiments, powder particle size was below 75 μm. Mixed powder for drug-loaded region was composed of APAP, HPMC, EC, PVP K30 and colloidal silicon dioxide in the ratio of 60:20:10:9.5:0.5 (w/w/w/w/w).

According to pre-experiments, the spacing of droplets within the direction of raster motion was 40 μm and the line-to-line spacing 100 μm. The velocity of printing was 0.4 × 12 (nL × kHz) and the thickness of one layer 200 μm with an interval time between two passes of 1 min. Sixteen millimeters was taken for the central distance among the DDDs and a batch of the product could produce 15 × 12 DDDs (Fig. 2). Other prototyping parameters of DDDs are listed in Table 1. For the F10 preparations another additional pass of binder I was deposited into the whole annular regions. For tablet F11, an additional two passes of binder I were deposited.

2.3. Properties of the DDDs

The properties of DDDs (weight, drug content, dose variation, hardness and friability) were determined as follows.

The weights of 20 DDDs were measured using an electronic balance (Sartorius, Germany). The mean value was then calculated. Twenty DDDs were ground to powder form using an agate pestle and mortar for drug content analysis. The ground powder (10 g) was transferred into a 1 L volumetric flask and dissolved in phosphate buffer solution (PBS, pH 6.8, 0.1 M) to prepare the assay samples for UV analysis. The content of the flask was shaken for 60 min and filtered through a 0.45 μm membrane filter (Millipore, USA). The resulting solution was appropriately diluted with PBS for UV analysis. Absorption at 257 nm was used to estimate the amount of APAP in the sample DDDs.

A total of six DDDs from different batches were tested in terms of content and content uniformity. Each DDD was individually weighed and then disintegrated and dissolved in PBS by shaking for 30 min. After filtration and dilution, absorbance at 257 nm was taken and the amount of APAP in each of the DDD was determined.

The mechanical strength of tablets is often used as a quality controlling parameter to ensure that the tablets are reproducible and can withstand the subsequent handling procedures. The mechanical properties of 3DP DDDs were evaluated by performing crush testing and friability testing. A YPJ-200B hardness tester (Shanghai Huanghai Drug Control Instrument Co. Ltd., Shanghai, China) was used to measure the crushing strength of tablets. Six DDDs were analyzed. The mean hardness was calculated and expressed in N/cm^2. The friability of 20 DDDs was determined using a 285 mm diameter, 39 mm wide drum friabilator (Tianjin University Radio Factory, China) at 25 rpm for 4 min. Test samples were carried out in triplicate. Friability was expressed in terms of weight loss and was calculated in the percentage (%, ±S.D.) of the initial weight.

2.4. Microscopy

The barrier layer and structure of DDDs F2 were observed on an environmental scanning electron microscope (ESEM, FEI Corporation, Hillsboro, OR). The DDDs were broken into two parts along the vertical cross-section. The sample was mounted on a metal stub with a double-side adhesive tape to be observed at 20 kV.

2.5. In vitro release tests

In vitro dissolution studies were carried out in a USP 23/NF 18 Apparatus II paddle system (Tianjin University Radio Factory, China) at 50 rpm in 900 mL of PBS at pH 6.8 and 37 °C. At 1-h intervals, samples (5.0 mL) were withdrawn from the dissolution medium and replaced with fresh medium to maintain a constant volume by means of injectors. After filtration through a 0.45 μm Millipore filter and dilution with PBS, samples were analyzed by a UV spectrophotometer (Unico Instrument Co. Ltd., Shanghai, China) at 257 nm. The amounts of APAP present in the samples were calculated from a reference standards calibration curve. APAP dissolved at specified time periods was plotted as the percentage released against time. All the measurements were carried out six times.

2.6. Morphology and erosion

To observe the morphological behavior of the DDDs during drug release process, six DDDs (F2) were placed in the same dissolution medium under the same conditions mentioned above. At predetermined time intervals, the samples were withdrawn and the images were recorded using a digital camera (Sony, Tokyo, Japan) to identify the location of the dissolution front as a function of time. The diameters of the DDDs and their inner holes were determined using a vernier caliper at different points of the release surface, and mean values were calculated. The DDDs were then returned to the dissolution baskets for continued testing.

The erosion rates of the DDDs were determined gravimetrically. At various time intervals the DDDs were removed from the baskets and dried at 50 °C under a vacuum until a constant weight was obtained. The measurements were repeated three times and the mean value was calculated.

Table 1
Prototyping parameters for preparing DDDs.

Formulation no.	*r* (mm), radius of aperture	*R* (mm), radius of DDD	Height (mm)	Additional passes
F1	**0.5**	5	5	0
F2	**1**	**5**	**5**	**0**
F3	**1.5**	5	5	0
F4	**2**	5	5	0
F5	1	**5.5**	5	0
F6	1	**4.5**	5	0
F7	1	**4**	5	0
F8	1	5	**6**	0
F9	1	5	**4**	0
F10	1	5	5	**1**
F11	1	5	5	**2**

Table 2
Properties of the DDDs.

Formulation no.	Weight (mg)	Dose (mg)	Variation of dose (%)	Hardness (N/cm^2)	Friability (%)
F1	368.6	222.4	2.7	68.4	0.72
F2	357.7	216.7	2.4	61.5	0.67
F3	339.1	204.2	1.8	60.7	0.66
F4	313.5	186.5	2.5	57.2	0.61
F5	436.2	267.4	3.7	54.6	0.74
F6	287.9	171.4	2.1	62.9	0.63
F7	224.1	132.5	1.3	63.7	0.58
F8	429.3	261.8	3.1	51.6	1.21
F9	286.3	172.6	2.1	63.7	0.71
F10	359.4	216.7	1.7	74.8	0.52
F11	363.2	217.3	1.2	86.4	0.37

3. Results and discussion

3.1. Properties of the DDDs

The mean weights, doses, dose variations, hardness and friability values were calculated and are shown (Table 2). All the DDDs exhibited fine pharmacotechnical properties and acceptable mechanical performance.

3.2. Barrier layer and structure

ESEM images of the barrier layer and the inner structure of the DDD are given in Fig. 3. It is obvious from Fig. 3a that the barrier layer was constant as a whole due to multi-passes of binder I, the mixed particles of the drug-contained region (Fig. 3a and b) were bound together through dissolution–re-solidification mechanisms and the interface between the barrier and the drug-loaded part was compacted.

DDDs are essentially multi-layered tablets with barrier layers on both bases. When traditional pharmaceutical technologies are employed, adhesion strength is always a concern in the fabrication process of multi-layered tablets, especially layers that are shaped individually (Abdul and Poddar, 2004). For example, barrier layers of the multi-layered matrix tablets made by direct compression was often detached from the tablets and failed to slow down the drug release when the dissolution processes were conducted. This is due to the poor adhesion strength and water insolubility to barrier layers (Sundy and Danckwerts, 2004). For multi-layered DDDs made by 3DP, this is not an issue as the strong adhesive forces between the barrier layers and the drug-contained regions resulted from the dissolution–re-solidification of the water-insoluble barrier powders during the printing process.

It is also evident that the inner structure of the drug-containing regions was uniform and compact (Fig. 3b). Due to the solubility of APAP in ethanol, wet dispensing of the drug as a solution may enable the final DDDs to include part of the drug existing in an amorphous state. This can facilitate the dissolution rate of a drug and will be beneficial to the stability and reproducibility of APAP release characteristics. In the 3DP process, the consolidation behaviors of the DDDs are different from that of the conventional direct-compressed or granulation procedures. The relationship between the consolidation mechanisms and the drug release deserves to be further studied.

3.3. Influence of the DDDs' geometrical dimensions on drug release profiles

The results of *in vitro* dissolution tests demonstrated influence of geometrical dimensions on drug release profiles. They showed (Figs. 4–7) that whatever the values of the prototyping parameters, all the DDDs could provide linear drug release profiles without any initial burst effect, or either any faster initial release rates. These are joint outcomes from the macro-doughnut-shape, multi-layered structure of the DDDs and local tailoring the concentration of drugs and release-retardant material.

From the results given in Fig. 4, it is clear that the total release time periods decreased as the diameters of the inner hole increased. The times taken to release 50% of the drug in F1, F2, F3 and F4 were 384, 306, 277 and 242 min respectively. This corresponded

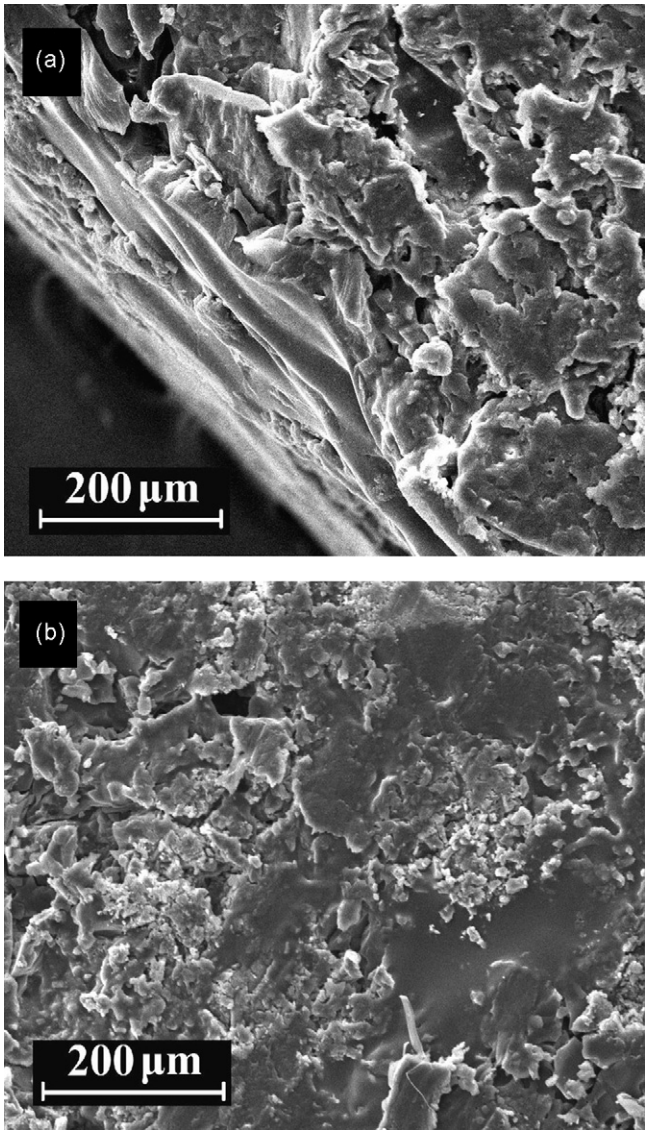

Fig. 3. ESEM images of DDDs' cross-section: (a) barrier layer and (b) inner structure.

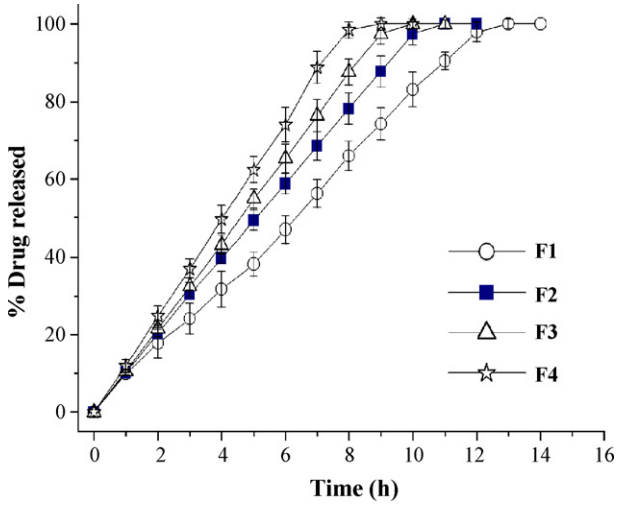

Fig. 4. Release profiles of APAP from the DDDs with different aperture diameters.

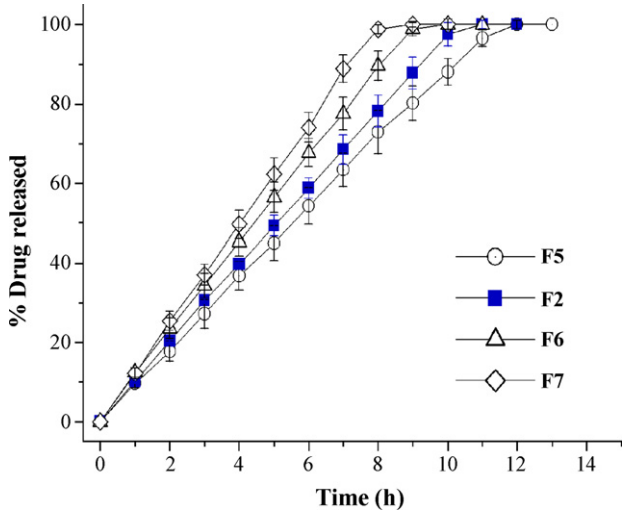

Fig. 5. Release profiles of APAP from the DDDs with different diameters.

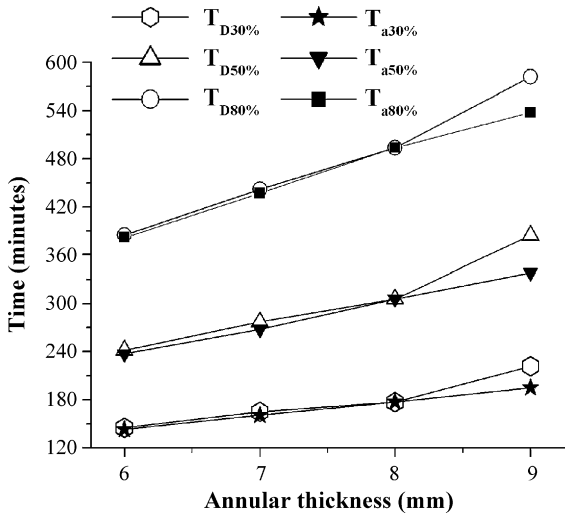

Fig. 6. Comparisons of release profiles of APAP from the DDDs with different annular thickness. $T_{D30\%}$, $T_{D50\%}$ and $T_{D80\%}$ represent the time periods taken to release 30%, 50% and 80% of the drug respectively from DDDs whose diameters kept a constant value of 10 mm. $T_{a30\%}$, $T_{a50\%}$ and $T_{a80\%}$ represent the time periods taken to release 30%, 50% and 80% of the drug respectively from DDDs whose diameters of central apertures kept a constant value of 2 mm.

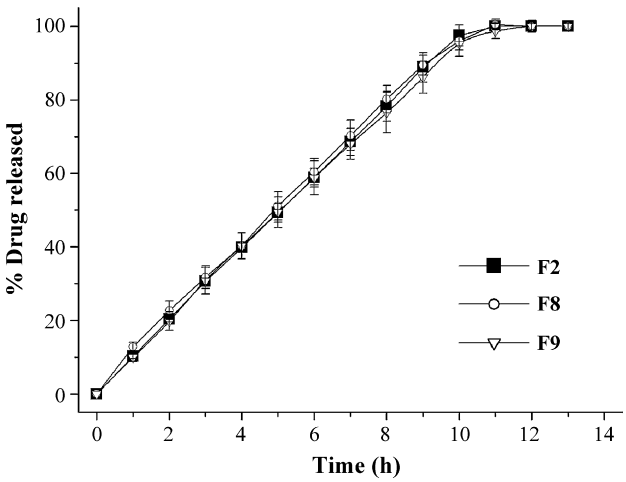

Fig. 7. Release profiles of APAP from the DDDs with different heights.

to the decrease of the annular thicknesses (4.5–3.0 mm). In Fig. 5, the total release time was prolonged as the diameters of the DDD increased. The time taken to release 50% of the drug (F7, F6, F2 and F5) were 237, 268, 306 and 338 min respectively; this corresponds to the increase of the annular thicknesses (3.0–4.5 mm).

The results that reflect the relationships between the release profiles of the DDDs and their annular thicknesses are shown as Fig. 6. Except for F1 which had an aperture diameter of 1 mm, the time periods taken to release 30%, 50%, 80% of the drug increased linearly with the increase in the annular thickness. DDDs with the same annular thickness exhibited the same release time periods regardless of DDDs diameters and the aperture diameters. As for F1, the apertures were clogged at the beginning of the dissolution tests and the erosion of inner surface was slower possibly due to swelling of HPMC.

As shown in Fig. 7, the release profiles were similar regardless of the DDDs height values of 4, 5 and 6 mm. There was no significant difference ($p > 0.05$, t-test) among the three DDDs, and the times taken to release 50% of the drug (for F2, F8 and F9) were 306, 295 and 303 min respectively. This illustrates that the total release time of DDDs is dependent on the annular thickness. Clearly the advantage of the system is that dosage in DDDs can be adjusted independently with little influence of the release profiles. This factor could be useful for the customisation of DDDs.

Thus, the annular thickness was a dominant factor for controlling the whole release time periods among the dimensional sizes of the doughnut-shaped DDDs. The dosage in the DDDs can be manipulated through the increase or decrease of the printing number of the drug-contained layers. The manufactured flexibility of 3DP makes it possible to offer new approaches to consider all types of solid formulations with complex design features and this will encourage the further development of controlled-release dosage forms using novel strategies.

3.4. The influence of different concentrations of EC on drug release profiles

Given in Fig. 8, release times of 50% of the drug for F2, F10 and F11 were 306, 342 and 415 min respectively. This corresponds to the number of printing passes of binder I (zero, once and twice). The higher the concentration of release-retardant materials EC in the drug-contained regions of the DDDs was, the slower the release rate and the longer the release time. This may provide some advantages in respect to the total release time periods, which could be adjusted independently by altering the passes of binder solution deposited into the whole annulus drug-loaded region. This obser-

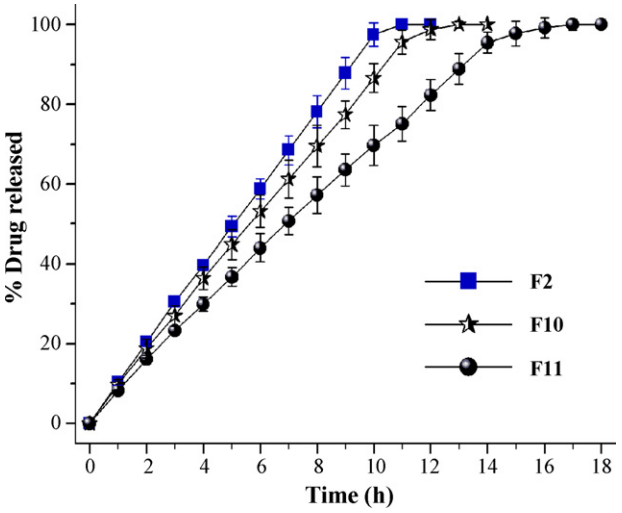

Fig. 8. Release profiles of APAP from the DDDs with different passes of binder solution containing EC.

vation may be useful for the design of future DDDs needed for individual therapy and applications.

EC was often incorporated into the hydrophilic matrix tablets to moderate the release pattern or release rate through the direct powder compression process or granulation methods. The release-retarding properties of EC in the hydrophilic matrix are mainly stemmed from two aspects: changing the penetration characteristics of the matrix tablets and reinforcing the intensity of the gel barrier through different types of interactions (Yu et al., 2007). However, the influence of EC on drug release in the hydrophilic matrix DDDs made by 3DP might be greater than tablets prepared by conventional methods.

EC could hinder the penetration of the solvent molecules into the tablets to some extent due to its insolubility in water both in tablets made by conventional methods and 3DP. However, the adhesive interactions between EC and HPMC in the two types of dosage forms are different. EC particles were loosely bound to HPMC particles in the tablets made by the powder compression method, or that different particles were simple enclosed and not bound together, with cracks or fissures (Traconis et al., 1997). In 3DP DDDs, strong adhesive interactions existed between EC and HPMC due to the dissolution–re-solidification of mixed powders and the EC remained from the binder I when the ethanol was removed after the binder was printing onto the layered powders. Thus the strong adhesive interactions will increase the strength of HPMC gels in the dissolution media and slow drug release for a prolonged period.

3.5. Morphology and erosion

The drug was released by means of HPMC E100 erosion, as APAP and EC had poor solubility in water (Karasulu et al., 2000). It is clear from Fig. 9 that the barrier layers remained in place and erosion occurred only from the outer curved cylindrical surface of the DDDs and the inner curved cylindrical surface of the apertures. During dissolution, the diameters of the apertures gradually increased while the diameters of the DDDs decreased until the drug-contained annulus was thin and could not withstand the action of the dissolution media. The DDD collapsed and was broken into two parts. However, the barrier layers were still connected with the drug-containing region, so demonstrating strong adhesive forces between them. This is consistent with the ESEM results.

Not only the EC layer was a barrier to water, it also remained in a solid state over the dissolution periods although they were very thin. Multi-layered tablets made by direct powder compression often have thick barriers, which might influence the dosage loading. Moreover, the barrier effects might be poor and time-dependent due to the barrier layers being progressively removed by the medium during the dissolution process. This is due to the weak interactions between the hydrophobic polymer particles (Sundy and Danckwerts, 2004; Conte and Maggi, 1996). Therefore, an increasing area of the planar surface of the drug-contained regions is exposed to interact with the outer environment and result in the time-dependent coating and release-retardant effect (Conte and Maggi, 1996). In DDDs manufactured using 3DP, the hydrophobic barrier layers were totally bound and kept their original form. This is due to the dissolution–re-solidification mechanism of the EC powders, which are the predominant binding mechanism (Wu, 1998).

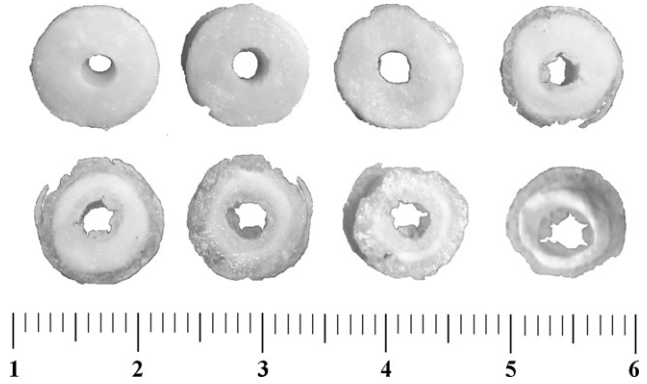

Fig. 9. Erosion photos of a DDD, appearance of the sample in 1–4, 6, 8–10 h.

There appeared to be a linear relationship between erosion time and DDD diameters, apertures diameters and DDDs' weights (Fig. 10). The regressed linear equations for the diameters of DDDs, the diameters of apertures and the DDDs' weights were:

$$D_D = 10.22436 - 0.45764 \times t \quad (r = 0.9975)$$

$$D_a = 1.928 + 0.3433 \times t \quad (r = 0.9895)$$

$$W = 360.9479 - 31.1887 \times t \quad (r = 0.9986), \text{ respectively.}$$

Here D_D denotes the diameters of DDD (mm), D_a apertures diameters (mm) and W represents the DDD' weight (mg).

It could be seen from the linear equations that the erosion rate of the outer surface of DDD was 0.4576 mm h^{-1}, this is a slightly larger than the rate of the inner aperture surface 0.3433 mm h^{-1}. However, this difference appears to have little influence on the linear release

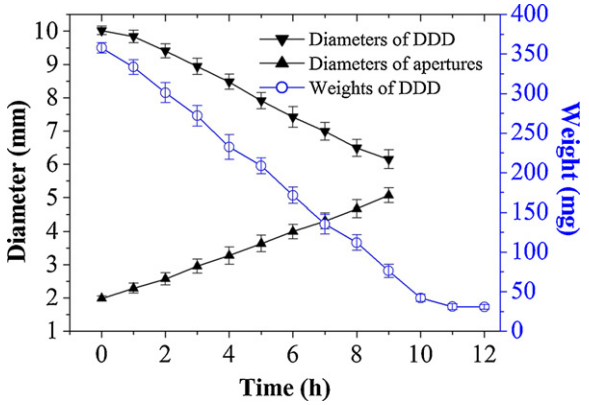

Fig. 10. Change of weights, diameters of the DDDs and diameters of the apertures with the erosion time.

kinetics of the drug loaded in the DDDs, which can be judged from the near linear loss of the DDD' weights.

4. Conclusion

Novel multi-layered doughnut-shaped DDDs with local variations of the drug and release-retardant materials for providing linear release profiles of a poorly water-soluble drug were developed and created using the 3DP process. Based on computer-aided design models, different DDDs containing the drug acetaminophen, the hydrophilic polymer HPMC and EC as release-retardant materials were prepared automatically by 3DP. Dispensing different binder solutions onto different powder regions during the printing processes carried out the tailoring of APAP and the release-retardant materials EC. Although the design features of DDDs were complicated, the production process was simple and easily repeated.

With EC, retardant materials, barrier layers provided both strong adherence forces with the drug-loaded regions and impermeable retarding effects of the drug release from the axial direction throughout the dissolution tests. Variations of local EC and drug concentrations were carried out to eliminate the faster initial release rates. *In vitro* dissolution experiments showed that the 3DP DDDs with different diameters, heights, EC concentrations and central aperture diameters, demonstrated linear release profiles. Moreover, morphological and erosion studies showed that drug release was through simultaneous surface erosion of the outer peripheries and inner apertures. The release time of the DDDs could also be manipulated independently by modifying the annular thicknesses or the passes of binder solution containing EC. The dosage of the DDDs could be adjusted independently by the heights of the DDDs, while the annular thicknesses and the heights of the DDDs could be easily controlled by 3DP prototyping.

3DP is a flexible and easy process that is highly suitable for manufacture. This system will provide novel strategies for studying and developing novel drug delivery devices, offering new approaches for preparing solid formulations involving complex design features for desired release profiles. 3DP may be capable of meeting the increasing demand from the pharmaceutical industry to invent and develop customised DDDs for individual therapy and application.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijpharm.2008.12.008.

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