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Microstructural investigation to the controlled release kinetics of monolith osmotic pump tablets via synchrotron radiation X-ray microtomography

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ABSTRACT

Tomographic imaging techniques are attractive tools for the visualization of the internal structural characteristics of pharmaceutical solid dosage forms. In this paper, the internal structure of the tablet core for a monolith osmotic drug delivery system, felodipine sustained-release tablet, was visualized via synchrotron radiation X-ray computed microtomography during the drug release process. The surface areas and three dimensional parameters of the tablet core were calculated based on the three dimensional reconstruction of the images. At different stages of the drug release process, the surface morphology, the hydration, the swelling, and the structure changing of the tablet, were visualized from the two dimensional monochrome X-ray images. The three dimensional volumes of the remaining tablet core correlated well with the percentages of felodipine ($R = 0.9988$). Also, the three dimensional surface area almost unchanged during the drug release process, which clearly demonstrated the intrinsic drug release mechanism of the osmotic drug delivery system. In conclusion, the synchrotron radiation X-ray computed microtomography, with rapid acquisition, high intensity and micro-scale spatial resolution, was found to be a useful tool for the quantitative elucidation of the intrinsic drug release kinetics and the three dimensional parameters such as surface areas of the remained core obtained by the synchrotron radiation. Thus, X-ray computed microtomography can be considered as a new and complimentary analytical tool to standard compendial pharmaceutical tests for quality control of osmotic drug delivery systems.

1. Introduction

The clinical performance of a drug molecule is not only dependent on its inherent therapeutic activity, but also largely dependent on the rate and extent with which it is delivered to the site of action by means of a drug delivery system (DDS) (Charman et al., 1999; Dwarakanadha and Swarnalatha, 2010). Oral controlled release systems hold the major market share because of the ease of administration and patient compliance. Well-designed drug delivery systems provide desired drug concentrations at the absorption site, maintaining the plasma drug level within the therapeutic range for a period of time, and thus can reduce the dosing frequency and adverse side effects to a minimum (Mehuys and Vervaet, 2010; Gupta et al., 2009a,b; Singh, 2007).

Among the various oral controlled drug delivery systems available, osmotic drug delivery systems (ODDS) delivering active agents by constant inner osmotic pressure, have attracted much interest since they have many advantages over other oral controlled drug delivery systems (Rose and Nelson, 1955). The zero-order drug release kinetics of ODDS is neither dependent on the drug chemical properties, nor the patient's physiological factors or concomitant food intake (Verma et al., 2000; Gupta et al., 2009a,b). However, the drug release kinetics of the ODDS shows dependency on formulation factors, including the solubility of drugs within the tablet core, the osmotic pressure of the core component(s), the semipermeable membrane characteristics, and the delivery orifice size (Verma et al., 2002).

Recently, advances have been made with the structural design of ODDS, from single chamber osmotic pumps to multiple chamber osmotic pumps (Malaterre et al., 2009). More than thirty ODDS

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products have been developed and launched in the market (Verma et al., 2004). More than two hundred patents and numerous publications have reported on the formulation aspects, clinical results and safety aspects of ODDSs (Santus and Baker, 1995; Kaushal and Garg, 2003; Kumar and Mishra, 2007; Conley et al., 2006; Bass et al., 2002). Whilst the structure is obviously the primary physical character of the ODDS, little research has been carried out to visualize the internal structure and internal dynamic changing of the ODDS tablet core during the drug release process.

The conventional in vitro dissolution tests for ODDS tablets with HPLC or LC/MS analysis can quantify the extent and rate of the drug release kinetics. The release profiles measured by conventional methods however do not provide the insight of the internal structure information of the ODDS tablet cores. Even though tight dissolution specifications are introduced to monitor the quality of the final products, a number of dosage forms fail after approval, and consequently have to be recalled from the market each year (Zeitler and Gladden, 2009). Thus, it is particular of interest to develop new methodologies to visualize the internal characteristics of the ODDS. When an internal structure method is established, the conventional in vitro release method can be calibrated. Modern in vitro tomography techniques are efficient tools which can directly reveal the internal structure and dynamic characteristics of the ODDS tablet core at different stages of the drug release process. This detail is not directly accessible by the conventional in vitro dissolution tests.

X-ray computed microtomography is a noninvasive technique, which can investigate the internal three dimensional (3D) structures of various objects. In pharmaceutical research, X-ray computed microtomography has been used to explore the fracture patterns of tablets prepared under different compositions and compaction pressures, and to determine the density distribution of tablets (Hancock and Mullarney, 2005; Ansari and Stepanek, 2006; Sinka et al., 2004; Chauve et al., 2007; Fu et al., 2006; Young et al., 2008; Wang et al., 2010a,b; Tokudome et al., 2009). Traini et al. studied the visualization of 3D structure of an ODDS tablet (Adalat OROS) using X-ray computed microtomography (CMT) (Traini et al., 2008). Tablets were analyzed successively in the CMT instrument under three different conditions: the first in the dry state, the second and the third after testing in the USP dissolution apparatus for 14 or 24 h, followed by drying in an oven at 50 °C for 1 h and immediately analyzed by CMT. Based on the reconstructed cross-sections, the authors modeled the void space in the tablet shell after drying the samples from the dissolution experiments. However, no quantitative data, such as the volume of the tablet core, were presented in their research.

With the availability of the synchrotron radiation light source, the synchrotron radiation X-ray computed microtomography (SR-μCT) is being introduced in pharmaceutical research. The synchrotron radiation light source is able to provide monochromatic X-ray with much higher photon flux (usually 2 orders of magnitude higher than conventional X-ray computed tomography) in relative parallel beam morphology, and SR-μCT permits the rapid acquisition of data with high intensity illumination and micro-scale spatial resolution via a high specification detector (Donath, 2007).

This study examined the internal 3D structure of monolith osmotic pump controlled release tablets using SR-μCT. The primary objectives are (i) to visualize the surface morphology, the internal 3D structure and their changing characteristics of the ODDS tablet core at different stages of the drug release process using a synchrotron radiation X-ray microtomography technique; (ii) to correlate the 3D steric data quantitatively with the remaining percentages of the drug in the tablet core and (iii) to elucidate the drug release mechanism of the monolith pump controlled release systems from the internal 3D steric data.

2. Experimental

2.1. Materials

Felodipine sustained-release tablets (Linuo®, each tablet containing 5 mg of felodipine) with orifices drilled on both sides were supplied by Hefei Lifeon Medication Group, China. The synchrotron radiation X-ray microtomography scans were acquired using the Shanghai Synchrotron Radiation Facility (SSRF) in Shanghai Institute of Applied Physics, Chinese Academy of Sciences (Shanghai, China). Data were analyzed using the commercially available software Image Pro analyzer (version 7.0, Media Cybernetics, Inc., Bethesda, MD, USA). Dissolution tests were carried out using Chinese Pharmacopoeia (Ch. P) Dissolution Apparatus II, (Tianjin TDTF Technology Co., Ltd., China). The chemical reagents used for the dissolution testing were of analytical grade and purchased from the Sinopharm Chemical Reagent Co., Ltd.

2.2. Methods

2.2.1. In vitro dissolution testing

In vitro drug release of the felodipine sustained tablet was measured using the basket method according to the Chinese Pharmacopoeia. The dissolution test was conducted with the rotation speed of 100 rpm, medium volume of 500 mL and at 37 °C. The dissolution medium was a phosphate buffer (pH 6.5) with 1% (w/v) sodium lauryl sulfate and was prepared as follows. 206 mL of 1 mol/L monobasic sodium phosphate monohydrate, 196 mL of 0.5 mol/L dibasic sodium phosphate anhydrous and 20 g of cetyltrimethylammonium bromide were transferred to a 5000 mL volumetric flask, diluted with water to volume, and mixed well (pH 6.5). 10 mL aliquot samples were withdrawn at 0.5, 1, 2, 3, 5, 6, 8, 10, 12 h and equivalent volumes of fresh medium were added to maintain sink conditions. The samples were then filtered and analyzed by UV at 361 nm (λ_{max} for felodipine).

2.2.2. Sample pretreatment

For metallic active pharmaceutical ingredients with relative high densities, such as ferrous sulphate, tablets containing these materials can be imaged directly using the SR-μCT technique (Young et al., 2008) during dissolution testing. The dissolution medium will not influence either the imaging or the visualization of the microstructure of the tablet core. However, for non-metallic drugs with similar density to the dissolution medium, like felodipine, the dissolution medium will interfere with the imaging (Karakosta et al., 2006). Unfortunately, most drugs are not metallic compounds. Therefore, tablets taken out from the dissolution medium must be dried prior to the image acquisition. In some published research, tablets are first frozen in liquid nitrogen or ultra low temperature refrigerator then dried using a freeze dryer (Chauve et al., 2007). We have considered using this method to dry the felodipine monolith osmotic pump tablet prior to the image acquisition. Due to the special structure of the monolith osmotic pump tablet and the fact that the volume expansion of water during the phase transition from liquid to ice when being frozen leads to the internally dissolved and suspension content of the drug in the tablet core being squeezed out at the initial freezing process, this procedure was not used. Furthermore, the remains of the tablet cores are mainly gels, and the formation of water crystals at low temperature may destroy the microstructure of the contents within the semi-permeable membrane. The deformation caused by any internal squeezing and possible crystal formation may devalue the applicability of the freeze-dry method to the osmotic pump tablets in this study.

For the SR-μCT test, 18 tablets were divided into six groups with three tablets in each group and the dissolution test was carried

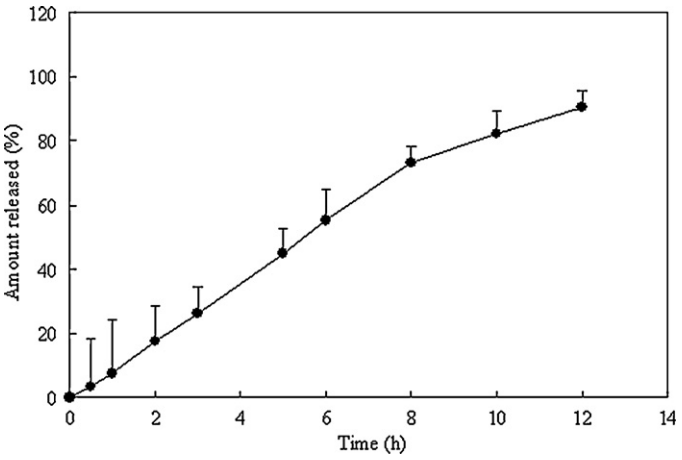

Fig. 1. The in vitro dissolution profiles of felodipine sustained release tablets ($n = 6$).

out. At 0.5, 1.0, 3.0, 6.0, 8.0 and 10 h, three tablets were taken out from the dissolution medium and carefully placed on a piece of flat, dry filter paper. In order to maintain the intrinsic structure of the tablet, the liquid on the surface and inside the tablet was absorbed as much as possible by the filter paper. Then, the tablet was kept at room temperature (with the relative humidity maintains at about 45%) for 24 h to remove the remaining residual liquid as possible.

2.2.3. SR-μCT tomography

SR-μCT tomographic images were acquired with beam line BL13W1 at Shanghai Synchrotron Radiation Facility (SSRF). Samples were scanned with synchrotron radiation at 13.0 keV. After penetration through the sample, the X-rays were converted into visible light by a YAG:Ce scintillator (200 μm thickness). Projections were magnified by diffraction-limited microscope optics (2× magnification) and digitized by a high-resolution 2048 pixel × 2048 pixel CCD camera (pco.2000, PCO AG, Kelheim, Germany). The pixel size was 3.7 μm, the exposure time was 4 s and the sample-to-detector distance was 25 cm. For each acquisition, 900 projection images were taken. Light field images (i.e. X-ray illumination on and the specimen out of the beam-path) and dark-field images (i.e. X-ray illumination off) were also collected during each acquisition procedure, in order to correct the electronic noise and variations in the X-ray source brightness.

The projected images at each time point of dissolution (0.5, 1.0, 3.0, 6.0, 8.0 and 10.0 h), were reconstructed using the software developed by SSRF to perform a direct filtered back-projection algorithm. The 3D rendered data were analyzed with VGStudioMax and Image-Pro 3D to obtain the qualitative and quantitative data, respectively.

3. Results and discussion

3.1. In vitro release kinetics of felodipine from the ODDS

The dissolution profile of felodipine sustained release tablets showed a typical osmotic pump release profile (Fig. 1). Within the earlier 8 h, the zero-order model provides a good correlation coefficient for the test formulations ($R = 0.9999$), suggesting that the release rate of felodipine remains approximately constant within 8 h.

Felodipine is a widely used as antihypertensive drug with poor aqueous solubility, less than 10 μg/mL at ambient temperature (Kerc et al., 1992). For drugs with moderate or poor aqueous solubility, the osmotic delivery system delivers a portion of the drug as a suspension (Wen and Park, 2010). The tablets tested in this study, Linuo®, are swelling monolithic osmotic tablets (MOTS) of felodipine containing a viscous suspending agent(s) (Lu et al., 2003; Liu et al., 2000).

The drug release mechanism of MOTS is different from that of an elementary osmotic pump tablet (EOP) or a push-pull osmotic pump tablet (PPOP) (Nokhodchi et al., 2008). In the dissolution medium, water is initially imbibed from the environment because of the difference in the osmotic pressure between the inside and outside of the semi-permeable membrane due to the presence of the osmotic agent. Then, a viscous drug suspension is formed in situ within the coated tablet, which is enabled by the presence of the suspending agent and the imbibed water. The suspension is subsequently pumped out through the orifices in the membrane as a result of the swelling of the suspending agent. The drug release is co-controlled by both the osmotic mechanism and suspension mechanism, which can be expressed by the Poiseuille's law of laminar flow (Eq. (1)).

$$\frac{dM}{dt} = \frac{\pi C}{8}\frac{R^4}{\eta}\frac{P_1 - P_2}{h} \quad (1)$$

where dM/dt is the drug release rate, C is the concentration of drug in suspension, R is the radius of orifice, η is the viscosity of suspension, $(P_1 - P_2)$ is the pressure difference between two sides of the semi-permeable membrane and h is the thickness of the semi-permeable membrane. As shown in Eq. (1), the drug release rate is directly proportional to C, R^4 and $(P_1 - P_2)$, and inversely proportional to η and h. Values of $(P_1 - P_2)$ and η are dependent on the suspending agent. In summary, the dynamic process of the drug release from MOTS can be linked to the osmotic, suspending and expanding properties of the tablet.

3.2. Visualization of the surface morphology and the internal 3D structure

Fig. 2 shows the 2D monochrome X-ray CT images of felodipine MOTS at different sampling time (0.5, 1.0, 3.0, 6.0 and 8.0 h). The semi-permeable membrane, the tablet core and the drug delivery orifices have been clearly visualized. The small voids generated during the tablet processing are also visible at the tablet core (image A). From Fig. 2 (image D at 3.0 h), it is also observed that the solid content is detached from the tablet core following erosion and swelling. The surface properties of the tablet shell maintain the original morphology at most of the sampling time points with evidence of some collapse at the surface of the tablet shells after 8.0 h dissolution testing.

As shown in Fig. 2, most of the tablet core remains as a solid or semi-solid form. Some cracks are seen at 0.5 and 1.0 h, whilst at 3.0 and 6.0 h, the tablet core becomes disaggregated and several voids form. The voids become increasingly larger adjacent to the drug delivery orifice. At 8.0 h, the entire content of the tablet core is nearly empty. It is interesting to observe that the shape of the remaining tablet core varies irregularly, which is very much different from the form and shape a formulation scientist might anticipate. It is also observed that some aggregates adhered to the internal wall of the tablet at 8.0 h and 10.0 h, which correlates in part with the release percentages of felodipine at 8.0 h and 10.0 h as 73.0% and 82.4%.

Fig. 3 shows the reconstructed 3D tomographic images at different drug release time points, demonstrating the dynamic changes in the internal 3D structure of the MOTS. The shape of the tablet is elliptic at 0.5 and 1.0 h. As a result of the hydration of the tablet core, the shape of the cores becomes more irregular with several voids after 3.0 h. Also, shape change is more pronounced adjacent to the delivery orifices, suggesting the release of felodipine near the delivery orifices is much faster than from other locations.

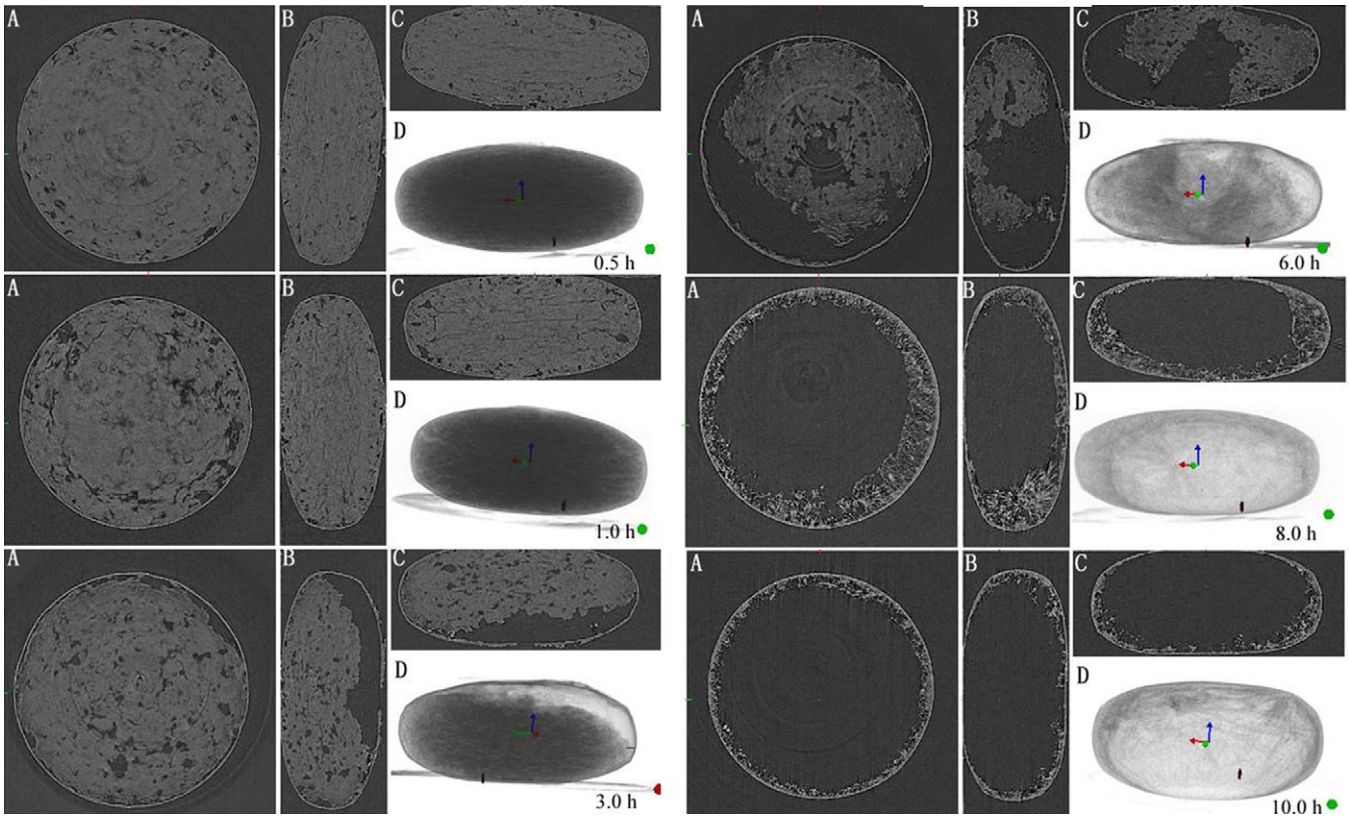

Fig. 2. 2D monochrome X-ray CT images of felodipine MOTS viewing from different aspects (A: top; B: front; C: back; D: the reconstructed image; air appears dark, grey represents the solid moiety of the tablet core, grey edge represents the semi-permeable membrane).

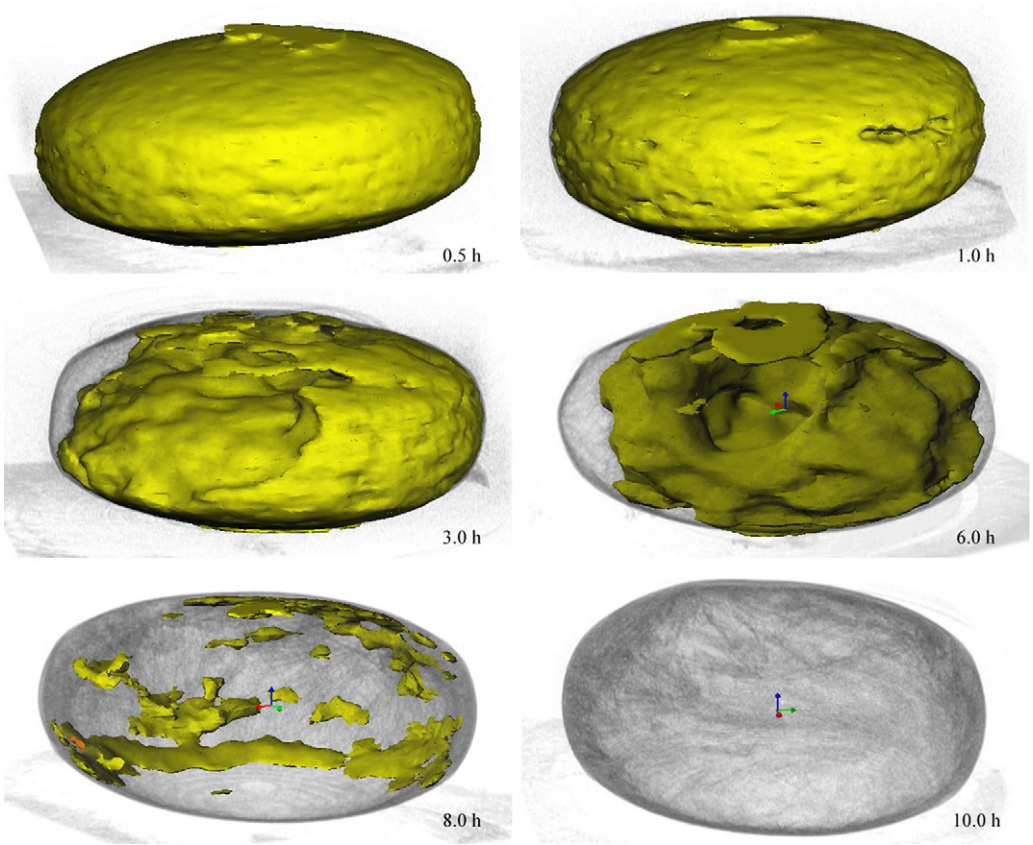

Fig. 3. Reconstructed three dimensional images of felodipine MOTS at different sampling time (yellow represents the solid moiety of the tablet core, air appears grey (after reconstruction, some moiety in Fig. 2 is not seen in Fig. 3)). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article).

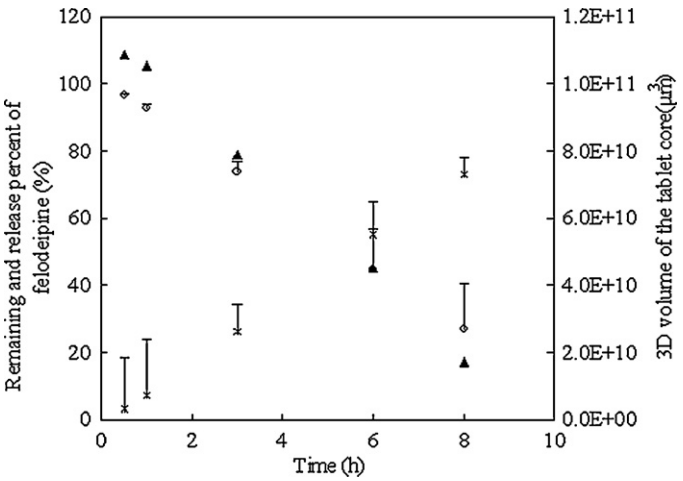

Fig. 4. Released percent and remaining percent of felodipine measured by in vitro dissolution testing plotted with 3D volume of the tablet core calculated from the reconstructed images ((*): the released percent; (○): the remaining percent; (▲): 3D volume of the tablet core).

In summary, based on the SR-μCT technique, the surface morphology, the internal 3D structure of the MOTS and their changing characteristics can be clearly visualized from the 2D monochrome X-ray CT images and the reconstructed 3D tomographic images.

3.3. Correlation between the 3D steric parameters and the remaining percentage of felodipine in the tablet cores

The volume and surface area of the remaining tablets core are calculated from the reconstructed 3D images (Fig. 4). The remaining percentages of felodipine MOTS in the tablet cores at 0.5, 1.0, 3.0, 6.0 and 8.0 h are calculated by taking 100% minus the in vitro release percent of felodipine (Fig. 4). As a result, the 3D volume values correlate well with the remaining percents of felodipine in the MOTS ($R = 0.9988$), suggesting that the 3D parameter accurately reflects the release characteristic of the felodipine MOTS.

For MOTS, the release of felodipine is co-controlled by the osmotic pressure and suspension. Initially, the pump is controlled by the osmotic mechanism, which is similar to the EOP systems. Water is imbibed and the suspension is created. Then, the core within the pump is covered by the liquid suspension. The remaining solid content of the tablet core (containing solid drug) is eroded. Fig. 5 shows two dimensional images of cross-sections of felodipine MOTS acquired at 3.0 and 6.0 h, which clearly suggests the erosion of the solid content from the tablet core to the suspension. As a result of the osmotic pressure and suspension co-mechanism, the suspension is pumped out through the orifice, a process which is also similar to the EOP systems.

Among these processes, the detachment of the solid content from the tablet core is complex. According to Eq. (1), for MOTS with zero-order drug release kinetics, values of R, η, $(P_1 - P_2)$ and h are nearly constant. However, the apparent value of C is dependent on the extent of solid content detached from the tablet core to the suspension. This is the erosion controlled process which can be expressed as Eq. (2) (Ketjinda et al., 2010).

$$\frac{dM}{dt} = \frac{DAC_s}{l} \tag{2}$$

where D, A, C_s, and l are the diffusion coefficient, the surface area of diffusion or erosion, drug solubility, and the thickness of boundary layer, respectively. For a given drug and tablet, values of D, l and C_s in Eq. (2) are invariable parameters. Therefore, the concentration of drugs in suspension in Eq. (1) is determined by A, the surface area of diffusion or erosion, namely, the surface area of the remaining tablet core.

Initial assessments might expect that the surface area as well as the volume of the tablet core would decrease with the disappearance of the solid content during the drug release process. It is observed in our study that the surface area of the tablet core during the drug release process only changes by a small amount. The shape of the internal solid content changes markedly from ellipse

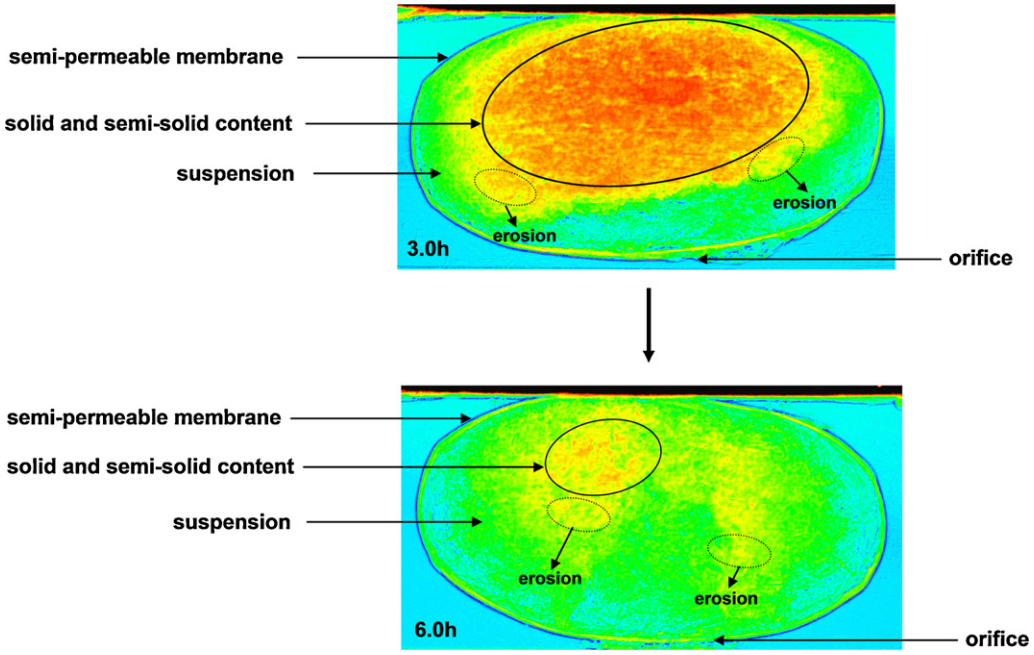

Fig. 5. Two dimensional images of the cross-sections of felodipine MOTS acquired at 3.0 and 6.0 h (demonstrating the erosion of the solid content from the tablet core to the suspension, red represents the solid moiety of the tablet core, yellow represents the semi-solid moiety of the tablet core, air appears blue, and green represents the hydration layer). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article).

to irregular with voids. This results in the 3D surface area values being almost constant.

In summary, values of C, R, η, $(P_1 - P_2)$ and h in Eq. (1) are all constant during the drug release process, which demonstrate the intrinsic mechanism of the drug release kinetics of the MOTS. Thus, the 3D surface area could be regarded as a key steric parameter for the quality control of felodipine MOTS products.

4. Conclusions

In this study, a new method combining X-ray tomography, image processing and 3D reconstructions was developed to research the drug release kinetics of felodipine monolithic osmotic tablets. The internal structure of the tablet core during the drug release process was clearly visualized from the 2D monochrome X-ray CT images and the 3D tomographic dynamic analysis. The 3D volumes of the tablets cores correlated well with the amount of drug remaining in the tablets. The 3D surface area was found to be almost constant, which is an important factor for the MOTS product quality control.

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