Research Article

Quantification of Swelling and Erosion in the Controlled Release of a Poorly Water-Soluble Drug Using Synchrotron X-ray Computed Microtomography

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Received 11 December 2012; accepted 13 May 2013; published online 16 July 2013

Abstract. The hydration layer plays a key role in the controlled drug release of gel-forming matrix tablets. For poorly water-soluble drugs, matrix erosion is considered as the rate limiting step for drug release. However, few investigations have reported on the quantification of the relative importance of swelling and erosion in the release of poorly soluble drugs, and three-dimensional (3D) structures of the hydration layer are poorly understood. Here, we employed synchrotron radiation X-ray computed microtomography with 9- μm resolution to investigate the hydration dynamics and to quantify the relative importance of swelling and erosion on felodipine release by a statistical model. The 3D structures of the hydration layer were revealed by the reconstructed 3D rendering of tablets. Twenty-three structural parameters related to the volume, the surface area (SA), and the specific surface area (SSA) for the hydration layer and the tablet core were calculated. Three dominating parameters, including SA and SSA of the hydration layer ($SA_{\text{hydration layer}}$ and $SSA_{\text{hydration layer}}$) and SA of the glassy core ($SA_{\text{glassy core}}$), were identified to establish the statistical model. The significance order of independent variables was $SA_{\text{hydration layer}} > SSA_{\text{hydration layer}} > SA_{\text{glassy core}}$, which quantitatively indicated that the release of felodipine was dominated by a combination of erosion and swelling. The 3D reconstruction and structural parameter calculation methods in our study, which are not available from conventional methods, are efficient tools to quantify the relative importance of swelling and erosion in the controlled release of poorly soluble drugs from a structural point of view.

KEY WORDS: drug release kinetics; gel-forming matrix tablet; statistical modeling; swelling and erosion; synchrotron radiation X-ray computed microtomography.

INTRODUCTION

Among a variety of oral controlled release drug delivery systems, water swellable matrix systems, particularly those containing hydroxypropyl methylcellulose (HPMC), are widely used because of the relative simplicity of formulation compositions, ease of manufacturing, and low cost, as well as

acceptance by regulatory authorities and applicability to drugs with a wide range of dose and solubility (1,2).

Much attention has been paid to the mechanism governing the transport of solutes. In recent review articles, mathematical models have been reviewed, which describe drug release from tablets with HPMC matrix (3,4). The diffusion equations for a semi-infinite medium were also proposed (5,6). Later, a model accounting for both the volume change of the swellable tablet upon contact with the aqueous medium and the countercurrent diffusion of the solute was also developed (7). Following the work on the swelling and dissolution behavior of the polymeric matrix systems (8,9), it has been found that the thickness of the continuously forming hydration layer upon water penetration was proportional to the square root of time when the swelling front was more rapid than the eroding front. The constant thickness of the hydration layer and zero-order drug release could be achieved when swelling and erosion fronts synchronized their movements (10). More recently, the importance of the diffusion front, the interface between the still undissolved drug, and the dissolved drug in the hydration layer, has also been stressed (11). The authors postulated that erosion of the matrix was the rate-limiting step for the release of poorly water-soluble drugs while for highly soluble drugs, the rate-limiting step was water penetration (12) or diffusion (13).

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The release profiles of the active ingredients in a liquid medium measured by conventional methods do not provide insight into internal microstructural changes on-going during drug release. A number of techniques with reported benefits and disadvantages have given some degree of insight into drug release from gelling matrix systems for polymer hydration, tablet swelling, and erosion. These techniques include optical imaging (14), ultrasound (15), magnetic resonance imaging (including MRI and NMR) (16), textural analysis (17), and vibrational spectroscopy (18). However, most of these studies are focused on the investigation of highly water-soluble drugs.

Recently, a quantitative ultra-fast MRI technique, together with ^{19}F NMR spectra and 1D ^{19}F profiles has been applied to study the dissolution process of the commercial HPMC matrix tablets (Fluvastatin sodium, Lescol® XL) (19). The ^{19}F 1D-MRI profiles from the hydration layer, with the pixel resolution along the axial length of 375 μm , show the transport activity of the drug inside the polymer matrix. The integration of the ^{19}F spectra is consistent with the drug release profile obtained from the UV measurement. However, this technique is limited by the spatial resolution of MRI (20–1,000 μm), being unable to provide the internal three-dimensional (3D) structure of the hydration layer, or the quantitative characterization of the hydration dynamics.

In this regard, modern synchrotron X-ray tomography techniques, with higher spatial resolution than MRI, are efficient tools to reveal directly the internal structure and dynamic characteristics of the hydration layer and the tablet core.

Synchrotron radiation X-ray computed microtomography (SR- μCT) has previously been used to explore the microstructural characteristics of tablet formulations indicating the fracture patterns of tablets prepared under different compositions and compaction pressures and to determine the density distribution of compressed dosage forms (20–24).

SR- μCT has also been employed to investigate tablet swelling in real time by following the movements of embedded glass microsphere tracers (25). Significant axial expansion has been observed, which may be due to mechanical relaxation of residual compaction stress. This expansion appears to be accompanied by extensive bubble formation, which may retard water penetration into the tablets. While this methodology can characterize the swelling behavior of gel-forming formulations in real time, water in the swelling medium may interfere with the image acquisition.

Our study aims to investigate temporal changes in the internal 3D structure of HPMC-based extended release tablets of felodipine (Plendil®; solubility of felodipine in water is 19.7 $\mu\text{g/mL}$) using SR- μCT and to gain improved mechanistic understanding of drug release. The primary objectives are (1) to visualize the surface morphology, the internal 3D structure of the hydration layer and the tablet at different stages of the drug release process using SR- μCT , (2) to study the effect of 3D volume and surface area-related parameters on drug release kinetics, and (3) to elucidate the drug release mechanism of HPMC-based controlled drug release systems through 3D hydration dynamic analysis and to quantify the relative importance of swelling and erosion using statistical modeling and SR- μCT .

MATERIALS AND METHODS

Materials

Felodipine extended release tablets (Plendil®, each tablet containing 5 mg of felodipine, lot number: 1010014) were produced by AstraZeneca PLC, China. In addition to the active ingredient felodipine, the tablets contained the following inactive ingredients: cellulose, red and yellow oxide, lactose, polyethylene glycol, sodium stearyl fumarate, titanium dioxide, and other ingredients. 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). Dissolution tests were carried out using Chinese Pharmacopoeia Dissolution Apparatus II (Tianjin TDTF Technology Co., Ltd., China). The chemical reagents used for the dissolution test were all of analytical grade and purchased from the Sinopharm Chemical Reagent Co., Ltd., China.

In Vitro Dissolution Testing

In vitro drug release of the felodipine-extended release tablets was measured using the paddle method according to the Chinese Pharmacopoeia. The dissolution test was conducted at a rotation speed of 100 rpm, medium volume of 500 mL at 37°C. The dissolution medium was a phosphate buffer (pH=6.5), which 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 5,000-mL volumetric flask, diluted with distilled water to volume, and mixed well (pH=6.5). Following addition of the tablet to the dissolution vessel, aliquot samples 10 mL were withdrawn from the dissolution vessel at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 7.0, 8.0, and 10.0 h and then replaced with equivalent volumes of fresh medium in order to maintain sink conditions since the solubility of felodipine in phosphate buffer (pH=6.5) containing 0.4% cetyltrimethylammonium bromide was 970 $\mu\text{g/mL}$ (26). The samples were then filtered with 0.45 μm microporous membrane and analyzed using a validated HPLC method to calculate the percent of felodipine released at different stages of the dissolution test. The HPLC analysis was performed on a Diamonsil C₁₈ column (150×4.6 mm, 5 μm ; Dikma Technologies, China) using methanol–water (80:20) as mobile phase, with a flow rate of 1.0 mL/min and injection volume of 20 μL . The detection wavelength was 238 nm. Calibration curves were prepared over the concentration range of 0.1, 1.0, 2.0, 5.0, 10.0, and 20.0 $\mu\text{g/mL}$. The linearity regression coefficient exceeded 0.995, showing a good linearity over this concentration range. Precision results revealed that the intra- and interassay RSD were below 1.0%, and the sample was stable over 24 h, with RSD below 1.0%.

Hydration and Erosion Studies by Gravimetric Analysis

The rate of uptake of the dissolution medium by the tablets and the rate of polymer erosion were determined by

gravimetric analysis methods. Dry matrix tablets were accurately weighed using a Mettler-Toledo ML-203 electronic balance (Mettler-Toledo, Inc.). In separate experiments, tablets were removed from the dissolution medium at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, and 10.0 h following exposure to the dissolution medium and lightly blotted with filter paper to remove excess water. The swollen tablets were weighed to determine the extent of water uptake and then dried in a convection oven at 40°C. After 12 h, the tablets were cooled to ambient temperature and then weighed. This measurement was termed the dried weight. All studies were conducted in triplicate. The percent increase in tablet weight that can be attributed to the uptake or absorption of water was calculated at each time point using Eq. 1. The percent matrix erosion was estimated at each time point using Eq. 2.

$$\text{Swelling percent} = \frac{W_s - W_i}{W_i} \times 100\% \quad (1)$$

$$\text{Matrix erosion percent} = \frac{W_i - W_t}{W_i} \times 100\% \quad (2)$$

where W_s is the weight of swollen samples at sampling times, W_i is the initial weight of tablet, and W_t is the weight of dried matrices at sampling times.

Samples Pretreatment for the SR- μ CT Scanning

In order to evaluate temporal changes in the microstructure of the matrix tablets during drug release by SR- μ CT test, 18 tablets were taken and divided into nine groups, each containing two tablets and a standard dissolution test was carried out. At 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, and 8.0 h, two tablets were removed from the dissolution medium and prepared for further testing.

Owing to the interference of the dissolution medium on the tablet imaging acquisition using SR- μ CT technique, tablets must be taken out from the dissolution medium and dried prior to image acquisition. Three methods have been reported for the pretreatment of the samples in SR- μ CT experiments: (1) drying in an oven, (2) freeze-drying, and (3) absorbing as much liquid as possible with dry filter paper and storage at room temperature over silica gel. For methods (1) and (3), the matrix gel tablet tended to shrink, and the gel formed on the surface of the tablet core would collapse causing changes to the internal gel structure during the long process. However, the freeze-drying method was found to maintain the microstructure of the hydration layer as much as possible with its rapid cooling process. After consideration of all three approaches, it was our view that the freeze-drying method caused minimal change to the structure of the tablet core and was selected for all further work.

In order to maintain the original shape of the tablets, swollen tablets were carefully removed using small spoons together with about 2 mL of the medium and placed individually in 24-well plates with 2 mL of the corresponding dissolution medium added to maintain the original shape of the tablets. The 24-well plates containing the tablets in various states of hydration and erosion were then immediately placed into the ultra-low-temperature refrigerator at -80°C for 12 h. After this

process, the tablets were freeze-dried over a period of 24 h at -50°C and 10 mTorr using a freeze dryer (FD5-3, China-GOLD SIM (Beijing) International Co. Ltd., China). These tablets were then kept in the dry cabinet under ambient temperature (relative humidity of 20%) for further SR- μ CT tests and were not reused in dissolution tests.

Synchrotron X-ray Microtomography

SR- μ CT tomographic images of prepared samples were acquired using beam line BL13W1 at the SSRF. Samples were scanned with synchrotron radiation at 13.0 keV. Images were recorded with an X-ray digital camera with direct coupled (micro)fiber-optic (Photonics Science Ltd, Robertsbridge, UK). The pixel size was 9 μm , the exposure time was 4 s and the sample-to-detector distance was 10 cm. For each acquisition, 720 projection images over 180° were taken. Flat- and dark-field images were also collected during each acquisition procedure, in order to correct the electronic noise and variations in the X-ray source brightness.

The projection sets of tablet for each time point of dissolution (0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, and 8.0 h) were reconstructed using developed software based on a filtered back-projection algorithm (27). The 3D-rendered data were analyzed with VGStudio Max and Image-Pro 3D to obtain qualitative and quantitative data, respectively. Statistical models were constructed with PASW Statistics version 18.0 (Polar Engineering and Consulting).

3D Parameter Calculations

After segmentation, slices were all converted into black and white images by removal of the background and noise. Then, 3D Iso-Surface models were constructed with segmented slices. The surface level, surface range and the simplification parameters were adjusted to optimize the models and to extract objects for further calculation of quantitative steric parameters.

RESULTS AND DISCUSSION

In Vitro Release Kinetics of Felodipine from the HPMC Matrix Tablets

Much attention has previously been paid to the mechanism governing drug release from hydrophilic matrices, where it has been suggested that the diffusion front at the interface between the undissolved drug and the dissolved drug in the hydration layer influences the rate of drug release from cellulose ether-based systems. In addition, water penetration and/or diffusion are postulated to be the rate limiting steps for the release of highly water-soluble drugs. For poorly water-soluble drugs, matrix erosion is considered to provide a major contribution to the mechanism of the drug release (28). Compared with studies about water-soluble drugs, few quantitative analyses have been reported on the detailed contribution of swelling and erosion to the release mechanism of poorly soluble drugs.

In vitro dissolution profiles of felodipine tablets are shown in Fig. 1a. In order to describe the drug release mechanism, n values are obtained from the following well-

Fig. 1. *In vitro* dissolution, hydration, and erosion of felodipine-sustained release tablets. **a** Dissolution profile. Error bars indicate the SD ($n=6$). **b** Percentage of weight gain (filled squares) and mass loss (filled triangles). Error bars indicate the SD ($n=3$). **c** 2D synchrotron X-ray radiography during drug dissolution. Error bars indicate the SD ($n=3$)

known equation proposed by Ritger and Peppas (29), as shown in Eq. 3.

$$\frac{M_t}{M_\infty} = kt^n \quad (3)$$

where M_t is the moiety of the drug released at time t , M_∞ is the moiety of drug released over a very long time that corresponds in principle to the initial loading, k is the kinetic constant and n is an exponent dependent on the release mechanism.

Since drug release occurs through the hydrophilic gel barrier around the tablets, the rate of drug release from the matrix is dependent on the formation and viscosity of the hydration layer and its swelling or erosion rate. For a cylindrical matrix, values of $n \leq 0.45$ indicate Fickian release, values $0.45 < n < 0.89$ indicate anomalous release kinetics (coupled diffusion/relaxation) and $n \geq 0.89$ indicate a zero-order release also known as purely relaxation controlled (erosion controlled) drug release. Studies of drug release from cylindrical matrices containing HPMC obtained values of the exponent n approximately 0.6 (30). When a soluble polymer is used, linear drug release is obtained and the value of the exponent n would be very close to 1.0, implying an erosion-controlled mechanism. In our study, the n value for the felodipine tablet is 1.09, indicating that erosion of the hydration layer is the dominant factor

determining the extended release of felodipine. Our results are also in full agreement with the reported findings that erosion is the controlling factor for poorly water-soluble drugs in hydrophilic HPMC matrices.

Hydration and Erosion Studies by Gravimetric Analysis

The gravimetric analysis is a conventional procedure to study the hydration and erosion of tablets. As a conventional method, data obtained from gravimetric analysis always exhibit relatively large errors and are used to demonstrate qualitative trends with regard to swelling and erosion. In this study, the gravimetric analysis is used as a qualitatively supplementary method to confirm that erosion is a critical factor in the controlled release of felodipine from the tested tablets.

Figure 1b shows the results of weight gain and mass loss of felodipine tablets. The swelling rapidly increases to a plateau, and then decreases over the course of the dissolution test. The curves of swelling and erosion intersect at the time point between 5.0 and 6.0 h, after which the tablets do not demonstrate any further swelling. However, mass loss occurs throughout the entire time course of the dissolution process. Furthermore, erosion kinetics appears to follow a similar pattern to those of drug release, suggesting that erosion is a critical factor influencing the controlled release of felodipine from the tablets tested.

Visualization of the Surface Morphology and the Hydration Layer of Felodipine Tablets

Synchrotron X-ray radiography image contrast is generated by absorption and phase shift of X-rays passing through the object of interest. In our set-up, the phase contrast is dependent on the sample-to-detector distance (in-line phase contrast). The short distance results in weak phase contrast. Thus, the contrast in our study is mainly from absorption of X-ray by the tablet matrix, including HPMC and small amounts of other lubricants containing elements such as sodium, aluminum, and silicon. With the increase in the degree of hydration, the associated swelling and erosion led to the hydration layer becoming more porous, which resulted in differences in the apparent density for different fronts. This enabled the unhydrated tablet core, the diffusion front, and the swelling front to be distinguished by the absorption contrast.

A set of two-dimensional monochrome projections is presented in Fig. 1c to show the surface morphology and the hydration layer of swollen felodipine tablets. The hydration layer, the glassy tablet core, the relative movement of the erosion, and swelling fronts with time, are clearly visible. The microstructures and the changes in the core can be observed. The HPMC matrix swells following absorption of water resulting in the increase of the matrix dimensions. After 0.5 h, the hydration layer is clearly observed and grows gradually with time. After 5.0 h, the hydration layer becomes thinner. The size of the glassy core reaches a maximum at 6.0 h and then reduces as the polymer hydrates to a greater extent. This phenomenon is also found in the results of the gravimetric analysis. After 8.0 h, the matrix is entirely hydrated with no core remaining. In the period from 1.0 h to 6.0 h, the thickness of the hydration layer exhibits only minor changes indicating the constant release rate of the felodipine HPMC matrix tablets.

Reconstructed 3D structures of felodipine tablets are created with segmented slices, as shown in Fig. 2a. The length, width, height, volume, and the surface area values of the whole tablet are shown in Fig. 2b. The length, width, and height of the tablet all increase within the first 1.0 h as the tablet swells following its contact with the dissolution medium. The length and width then start to decrease from 2.0 h onwards as the HPMC matrix erodes. The height of the tablet, however, remains the same. The volume and surface area of the tablet diminish with time.

The total projected images are reconstructed using the software developed by SSRF to perform a direct filtered back-projection algorithm (27). In order to enhance the quality of reconstructed slices, the X-TRACT SSRF CWS x64 (Commonwealth Scientific and Industrial Research Organization, Australia, <http://www.ts-imaging.net/Default.aspx>) is used for phase contrast extraction. The reconstructed slice stack is converted into 8-bit grayscale format and re-sliced vertically. Then, the vertical slices of tablets at different time points (include the well hydrated tablets and the tablet with totally dried core) are analyzed to determine the threshold gray values to distinguish the erosion front, the diffusion front and the swelling front. The quantitative criterion to distinguish the erosion front, the diffusion front and the swelling front is exemplified by the sample at 0.5 h (Fig. 3). As shown in Fig. 3, the completely hydrated erosion layer has a gray value from the background value from 18

to the value of 100; the gray value between 100 and 150 is the partially hydrated hydration layer and the glassy layer has a gray value above 150. Thus, the front with gray value of 18 is the erosion front, that with a value of 100 is the diffusion front, and the swelling front is shown by the layer with a grey value of 150. The intermediate portion between the erosion front and the swelling front is the hydration layer.

The quarter view of the hydration layer is shown in Fig. 4 together with the volume of the hydration layer and the surface area of the hydration layer. The reduction in volume of the hydration layer is slower than that of the whole tablet, indicating the drug release rate determining influence of matrix erosion.

In summary, based on the SR- μ CT technique, changes in the surface morphology, the internal 3D structure of the tablets, and the hydration layer can be clearly visualized from the 2D synchrotron X-ray radiography and the reconstructed 3D tomographic images.

Correlation of the 3D Hydration Parameters with Drug Release Kinetics

As shown in Fig. 3, the X-ray absorption of the glassy core is stronger than that of the hydration layer. The density of the hydration layer is lower than that of the glassy core as the hydrated matrix is much more porous after the uptake of the dissolution medium. From these observations, it is possible to distinguish the hydration layer from the glassy core based on the X-ray intensity. Thus, the hydration layer has been extracted from the 3D models, and the quantitative parameters have been calculated accordingly.

As a result, 23 3D steric parameters have been calculated based on the extracted Iso-Surface models in this study. The names, descriptions, and the units of these parameters are listed in Table I.

With regard to correlations between single parameters and drug release kinetics, it is reported that the volume and surface area-related parameters of the tablet are key variables in controlling drug release from HPMC matrix tablets (31). Therefore, correlation between volume and cumulative release percent has been investigated, as shown in Fig. 5a–c. All the volume parameters, including volume of the whole tablet, volume of the glassy core, and volume of the hydration layer, correlate to a good degree with percentages of drug release ($R^2=0.90, 0.94$, and 0.81 , respectively). Generally, the correlations of each volume parameter to the cumulative release percentages are better than that of the single surface area parameters.

Different from the routine quality control indicators of the cumulative release percentages, drug release rate (dM/dt) values provide the key characteristics of drug delivery systems. Thus, the correlations between surface area parameters and drug release rate are shown in Fig. 5d–f. The R^2 values for these correlations are 0.45 for the surface area of the tablet and 0.80 for the surface area of the hydration layer, while the R^2 value between the surface area of the glassy core and the release rate is 0.87 , indicating that the surface area of the glassy core is one of the key factors in determining constant drug release. Namely, the matrix swelling has an important and controlling effect on the drug release kinetics.

In addition, a statistical model was constructed using SPSS PASW statistics (version 18.0) for the multivariate analysis, using drug release rate as the dependent variable ($n=9$). The

Fig. 2. Changes to internal structures of the whole tablet during drug dissolution. **a** Reconstructed 3D images. **b** Length (filled diamonds), width (filled squares), and height (filled triangles). **c** Volume (empty diamonds) and surface area (empty squares) values

sample of 0 h was excluded as the value of specific surface area at 0 h cannot be calculated. Independent variable reduction was carried out with the consideration of the value of R^2 , the equation significance, the parameter coefficient significance,

and physical meaning of the variables. Three parameters with notable influence on the drug release from felodipine tablets were identified from 23 3D structural parameters by independent variable reduction.

Fig. 3. The quantitative criterion to distinguish the erosion front, the diffusion front, and the swelling front with the line profile of vertical slice of the sample at 0.5 h (the front with gray value of 18 is the erosion front, 100 is the diffusion front, and 150 is the swelling front; the intermediate portion between the erosion front and the swelling front is the hydration layer)

Based on the three selected parameters, a multiple-linear regression model was established, as given in Eq. 4.

$$\frac{dM}{dt} = 420.4 \cdot SA_{\text{hydration layer}} + 128.4 \cdot SA_{\text{glassy core}} + 214.9 \cdot SSA_{\text{hydration layer}} - 23.4 \quad (4)$$

The $SA_{\text{hydration layer}}$ is the surface area of the hydration layer, which includes the areas of pores and channels inside the hydration layer. The $SA_{\text{glassy core}}$ is the surface area of the nonhydrated glassy core, which is the interface where the glassy core swells into gel and hydration occurs. The $SSA_{\text{hydration layer}}$ is the specific surface area of the hydration layer (as shown in Table I; Fig. 6), which reflects the magnitude of the hydration layer. All the relevant parameters in Eq. 4 have been normalized to ensure that all parameters have equal determinant strength to drug release rate. The

statistical model exhibits relative desirable predictability, with $R^2=0.96$ and significant p values (<0.001).

Relative Importance of Swelling and Erosion in Controlled Release of Felodipine

Limited research has been reported to quantify the relative importance of swelling and erosion to the controlled release of poorly water-soluble drugs. Bettini *et al.* have studied the release mechanisms of drugs with different solubilities (bufomedil pyridoxalphosphate with water solubility of 65% (w/v), sodium diclofenac with water solubility of 3.1% (w/v), nitrofurantoin with water solubility of 0.02% (w/v)) from HPMC matrices (32). The role played by polymer swelling in drug transport was demonstrated with two different swelling/release experiments. The results showed that the tendency of the matrix to erode increased as drug

Fig. 4. Visualization and quantitative analysis of the hydration dynamics during drug dissolution. **a** Reconstructed 3D images of the hydration layer. **b** Volume (asterisk) and surface area (filled squares) values of the hydration layer

Table I. The Names, Descriptions, and the Units of the 3D Parameters

3D parameters	Description	Units
Volume of tablet	Volume of the whole tablet	μm^3
Volume of core	Volume of the unhydrated core	μm^3
Volume of hydration layer	Volume of the hydrated gel layer	μm^3
Surface of tablet	Surface area of whole tablet	μm^2
Surface of core	Surface area of unhydrated core	μm^2
Surface of hydration layer	Surface area of the hydrated gel layer	μm^2
Specific surface of tablet	Surface area of tablet/volume of tablet	μm^{-1}
Specific surface of core	Surface area of core/volume of core	μm^{-1}
Specific surface of hydration layer	Surface area of tablet/volume of tablet	μm^{-1}
Porosity of hydration layer	The volume of voids over the total volume	%
Length of whole tablet	Size of bounding box in Y direction	μm
Width of whole tablet	Size of bounding box in X direction	μm
Height of whole tablet	Size of bounding box in Z direction	μm
Box ratio of whole tablet	Ratio between the maximum and the minimum size of the bounding box	Dimensionless
Box ratio of core	Ratio between the maximum and the minimum size of the bounding box	Dimensionless
Sphericity of whole tablet	A measure of how spherical an object is	Dimensionless
Sphericity of core	A measure of how spherical an object is	Dimensionless
Surface deviation of tablet	Deviation of normal vectors on surface	Dimensionless
Surface deviation of core	Deviation of normal vectors on surface	Dimensionless
Volume fraction of tablet	Ration of object's volume to the box volume	Dimensionless
Volume fraction of core	Ration of object's volume to the box volume	Dimensionless
Diameter of tablet	Equivalent diameter of whole tablet	μm
Diameter of core	Equivalent diameter of unhydrated core	μm

solubility decreased. In swellable matrices loaded with sparingly or slightly soluble drugs, solid drug particles can be transported within the hydration layer by polymer swelling. The presence of solid particles in the gel reduced the swelling and the entanglement of polymer chains and affected the resistance of gel towards erosion. As a consequence, the matrix became more erodible. The rate and amount of drug released from swellable matrices were dependent not only on the drug dissolution and diffusion

but also on solid drug translocation in the gel because of polymer swelling.

It can be observed from Eq. 4 that the significance order of the independent variables is $SA_{hydration\ layer} > SSA_{hydration\ layer} > SA_{glassy\ core}$. These three parameters represent the interface where the erosion and swelling of the hydrophilic matrix occur. The first two parameters represent the contribution of matrix erosion to controlled drug release while the last one represents the contribution of matrix swelling. Based

Fig. 5. Correlation between the steric parameters and drug release kinetics

Fig. 6. Schematic diagram of the swelling front, the diffusion front, and the erosion front of felodipine HPMC tablet during drug dissolution

on the quantitative relationship between 3D hydration parameters and drug release kinetics, drug release rate is determined primarily by matrix erosion, whereby the matrix swelling coexists. This finding is in accordance with the reported evidence that the matrix erosion governs the transport of poorly soluble drugs from the hydrophilic controlled drug release systems. Importantly, this model provides details of the quantitative contribution of matrix erosion and swelling to drug release rate for poorly water-soluble drugs with 3D hydration parameters that cannot be measured by conventional methods. Thus, the release mechanism is identified as a combination of erosion and swelling.

In our study, the relative importance of swelling and erosion in the controlled release of felodipine is quantified through the application of a statistical model and SR- μ CT. The solubility of felodipine in the dissolution medium is 970 $\mu\text{g/mL}$ (0.097%, w/v), which is relatively close to the low level solubility (0.02%, w/v) in Bettini *et al.*'s study (32). Although different techniques are used in these two studies, consistent results are obtained, the release of poorly water-soluble drugs from HPMC matrix being dominated by erosion and swelling. Furthermore, 3D structures of the hydration layer revealed in our study by SR- μ CT with high resolution (9 μm) provides additional insight into the internal architecture of the swellable matrices as well as additional quantification of events controlling drug release. The 3D reconstruction and structural parameter calculation methods detailed above are effective tools to visualize and quantify the translocation of drug particles in HPMC matrix hydration layers from a structural point of view.

Among 23 structural parameters, three key parameters have been selected with variable reduction to establish and optimize the statistical regression model, which covers nine data points over the release profile. For the constant release of felodipine during the sampling time period and limited SR- μ CT beam time available, samples were obtained at nine time points to obtain as much data as possible from the imaging acquisition. Thus, only a small sample model has been established by this report, a large-scale modeling or a real-time structure

reconstruction, although challenging, would provide further in-depth information and knowledge. Nevertheless, the correlation coefficient (R^2) and the significance value (p) for the regression model are statistically significant.

Several imaging approaches have been employed to explore the hydration layer change during drug release. Among them, SR- μ CT can provide high spatial resolution. However, as the X-ray attenuation coefficient of water is similar to that of polymer material in the tablet, the image contrast would be significantly affected when tablets are placed in aqueous dissolution medium. To overcome this drawback, the tablets were dried with the method which caused minimal change to the structure of the tablet core in our study. In addition, it is desirable to employ complementary methods to clarify chemical composition for the structural information obtained by SR- μ CT, such as using MRI to identify the water content change or using matrix-assisted laser desorption/ionization to identify the distribution of drug in the tablet core and the gel layer.

CONCLUSIONS

In this study, a new method combining synchrotron X-ray tomography, image processing, and 3D reconstructions has been developed to study the drug release kinetics and to quantify the relative importance of swelling and erosion to the controlled release of felodipine from HPMC matrix tablets. The surface morphology, the internal 3D structure of the tablets and the hydration layer dynamic characteristics can be clearly visualized from the 2D monochrome X-ray CT images and the reconstructed 3D tomographic images. The established statistical model of the 3D hydration parameters has demonstrated that the erosion of the hydration layer of the hydrophilic matrix together with the swelling are the rate controlling factors for felodipine release.

ACKNOWLEDGMENTS

We are grateful for the beam time granted from the SSRF Key Program (Z12sr0040) and the financial support from the Ministry of Science and Technology of China (S2010GR0920, 2010ZX09401-402, and 2012ZX09301001-001), the Chinese Academy of Sciences Visiting Professorship for Senior International Scientists (Prof. Peter York) and the National Natural Science Foundation of China (81273453).

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