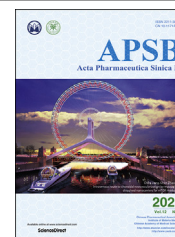




Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com



ORIGINAL ARTICLE

Redefinition to bilayer osmotic pump tablets as subterranean river system within mini-earth *via* three-dimensional structure mechanism



Abi Maharjan^{a,b,c,†}, Hongyu Sun^{a,d,†}, Zeying Cao^{a,c}, Ke Li^{c,e},
Jinping Liu^f, Jun Liu^{a,g}, Tiqiao Xiao^e, Guanyun Peng^e, Junqiu Ji^g,
Peter York^a, Balmukunda Regmi^h, Xianzhen Yin^{a,g,*},
Jiwen Zhang^{a,c,d,*}, Li Wu^{a,b,*}

^aCenter for Drug Delivery System, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China

^bSchool of Pharmacy, Key Laboratory of Molecular Pharmacology and Drug Evaluation, Ministry of Education, Yantai University, Yantai 264005, China

^cUniversity of Chinese Academy of Sciences, Beijing 100049, China

^dNMPA Key Laboratory for Quality Research and Evaluation of Pharmaceutical Excipients, National Institutes for Food and Drug Control, Beijing 100050, China

^eShanghai Synchrotron Radiation Facility/Zhangjiang Lab, Shanghai Advanced Research Institute, Chinese Academy of Sciences, Shanghai 201204, China

^fHefei Lifeon Medication Group, Hefei 230088, China

^gCenter for MOST and Image Fusion Analysis, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201210, China

^hMaharajung Medical Campus, Institute of Medicine, Tribhuvan University, Kathmandu 44606, Nepal

Received 10 August 2021; received in revised form 11 October 2021; accepted 24 October 2021

KEY WORDS

Bilayer osmotic pump tablet;
Synchrotron radiation micro-computed

Abstract Defining and visualizing the three-dimensional (3D) structures of pharmaceuticals provides a new and important tool to elucidate the phenomenal behavior and underlying mechanisms of drug delivery systems. The mechanism of drug release from complex structured dosage forms, such as bilayer osmotic pump tablets, has not been investigated widely for most solid 3D structures. In this study, bilayer osmotic pump tablets undergoing dissolution, as well as after dissolution in a desiccated solid state were

*Corresponding authors. Tel./fax: +86 21 20231980 (Li Wu); +86 21 20231980 (Jiwen Zhang); +86 2150805622 (Xianzhen Yin).

E-mail addresses: xzyin@simmm.ac.cn (Xianzhen Yin), jwzhang@simmm.ac.cn (Jiwen Zhang), wuli@simmm.ac.cn (Li Wu).

[†]These authors made equal contributions to this work.

Peer review under responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

<https://doi.org/10.1016/j.apsb.2021.11.008>

2211-3835 © 2022 Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

tomography;
Three-dimensional
microstructure;
Release kinetics;
Void formation;
Peripheral “roadways”;
Push-pull model;
Subterranean river model

examined, and visualized by synchrotron radiation micro-computed tomography (SR- μ CT). *In situ* formed 3D structures at different *in vitro* drug release states were characterized comprehensively. A distinct movement pattern of NaCl crystals from the push layer to the drug layer was observed, beneath the semi-permeable coating in the desiccated tablet samples. The 3D structures at different dissolution time revealed that the pushing upsurge in the bilayer osmotic pump tablet was directed *via* peripheral “roadways”. Typically, different regions of the osmotic front, infiltration region, and dormant region were classified in the push layer during the dissolution of drug from tablet samples. According to the observed 3D microstructures, a “subterranean river model” for the drug release mechanism has been defined to explain the drug release mechanism.

© 2022 Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

A therapeutic effect is attained when a drug released and absorbed from a dosage forms reaches the biologic target within the therapeutic window at a predetermined time. To produce effective therapeutic responses without causing significant adverse effects in patients, various dosage forms have been designed. Among them, oral drug delivery is one of the most common and convenient routes for drug administration in clinical practice. The releasing rate and extent from conventional oral dosage forms could not be controlled for attaining constant therapeutic level^{1,2}. Moreover, bioavailability from these formulations could be easily affected by the physiological factors like food, gastric motility, and pH³. The above shortcomings can be overcome by formulating controlled and sustained drug release dosage forms such as osmotic pump tablets⁴, multi particulate⁵, and erosion controlled drug delivery systems⁶. Osmotic pump tablets have been shown to be an attractive tool for oral controlled drug delivery system⁷ with different osmotic devices invented over the past 60 years⁸. Osmotic pump tablets are efficient formulations with a simple arrangement to achieve zero-order drug release by generating hydraulic pressure *via* a swelling osmotic agent inside the tablets⁹. Different types of osmotic pump tablets have been reported such as elementary osmotic pump tablets¹⁰, controlled porosity osmotic pump tablets¹¹, sandwiched osmotic pump tablets¹², capsule-based osmotic systems^{13,14}, and push–pull osmotic pump (PPOP) tablets¹⁵. Among them, PPOP tablets have received much attention for its success in delivering drugs with low aqueous solubility^{16,17}.

Various imaging techniques such as micro-computed tomography (μ CT)¹⁸, magnetic resonance imaging (MRI)¹⁹, terahertz imaging²⁰, confocal imaging technique and Raman imaging²¹ facilitate *in situ* visualization of solid dosage forms, offering understanding of ongoing microstructural transformations in different conditions. The μ CT imaging offers special features for non-destructive reconstruction of specimens at micrometer resolution; MRI applies magnetic field gradients and radio waves to generate the 3D images; terahertz imaging finds its application in studying semiconductor material properties, biomedical cell imaging and structures of pharmaceutical dosage forms. The confocal imaging technique is useful for tracking fluorescence material within the specimens. Raman imaging allows observation of molecular distribution and dynamic behaviors in the specimens. Direct comprehensive visualization in submicron resolution in any section and detailed microstructure analysis are the challenging aspects in all of the above methods.

Synchrotron radiation micro-computed tomography (SR- μ CT) is an advanced technology that uses synchrotron radiation X-rays having high photon flux and polarization as a light source to achieve high-speed imaging, high energy, and high spatial resolution. It is a valuable investigational tool for non-destructive *in situ* three-dimensional (3D) visualizations of samples. Moreover, this technology allows sectioning the sample in any direction for the direct visualizations of the internal structure at micrometer resolution. It has been used in pharmaceuticals to reveal key information about the structure of active pharmaceutical ingredients (API) and dosage forms^{22–24}, drug release kinetics²⁵, drug characterization²⁶, and the quality of pharmaceutical products²⁷.

The underlying principle of drug delivery through an osmotic pump system involves the controlled diffusion of water through a semi-permeable membrane (surrounding the tablet unit) and drug release through a drilled orifice^{28,29}. For monolith osmotic pump tablets, the 3D structures²⁴ and the controlled release kinetics^{25,30} have been investigated based on SR- μ CT. Due to the complex geometry of PPOP tablets, the various microstructural transforms occur within the tablets which may impede or promote drug release kinetics. This aspect has not been considered to date in defining drug release models from PPOP tablets.

A clear understanding regarding the release kinetics of PPOP tablets with associated microstructural alteration has not been established. In this study, dissolution conditioned bilayer osmotic pump tablets before and after desiccation were investigated *via* SR- μ CT to discover detailed microstructural transformations at different drug dissolution times. Static and dynamic structures of bilayer osmotic pump tablets were characterized comprehensively. Based on observed *in situ* structures, a new release model for the bilayer osmotic pump tablets is presented which defines the drug release mechanism.

2. Materials and methods

2.1. Materials

Bilayer osmotic pump tablets (Cardura® XL) were purchased from Pfizer Inc. (Batch number R61208, Wuxi, China), containing doxazosin mesylate as an active ingredient, with polyethylene oxide (PEO), sodium chloride (NaCl), hydroxyl propyl methylcellulose (HPMC), red ferric oxide, titanium dioxide, magnesium stearate, cellulose acetate, Macrogol®, pharmaceutical glaze, and black iron oxide as inactive ingredients. Synchrotron radiation was applied for obtaining the micro-computed tomography scans from

Shanghai synchrotron radiation facility (SSRF) in Shanghai Institute of Applied Physics, Chinese Academy of Sciences (Shanghai, China). Different software programs including Phase-sensitive X-ray Image Processing and Tomography Reconstruction (PITRE, Version 3.1), Image-Pro Plus (Media Cybernetics, Version 6), Image-Pro Premier 3D (Media Cybernetics, Version 9.1), and Amira (Thermo Fischer Scientific, Version 5.6) were used for obtaining different qualitative and quantitative information of the tablets²⁷. Dissolution tests were carried out according to *United State Pharmacopoeia* (USP, 2017), using dissolution apparatus II (Distek Model 2500, Distek Inc., North Brunswick, USA). The chemicals used for the dissolution test were of analytical grade and purchased from the Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). Water was purified by a reverse osmosis using Milli-Qs system (Millipore, Bedford, MA, USA).

2.2. *In vitro* dissolution test

In vitro drug release of Cardura® XL was measured using the paddle method at a rotation speed of 50 rpm according to USP 2017 ($n = 6$). The dissolution media was simulated gastric fluid, without enzyme at pH 1.2 at 37 °C. Following the addition of the tablets in the dissolution vessel, 2 mL of the aliquots were withdrawn from the dissolution vessel at the predetermined time points as 1, 2, 4, 6, 8, 12, and 16 h. The withdrawn samples were immediately filtered using a microporous membrane with the pore size of 0.22 μm and also, an equal volume of dissolution medium was replaced in the dissolution vessel to maintain sink condition. The concentration of the doxazosin mesylate at each time point was analyzed by using high-performance liquid chromatography (HPLC, Agilent, 1290, USA) on column Platisil (C18, 250 mm \times 4.6 mm, 5 μm , Agilent Technologies, USA). Buffer solution for mobile phase was prepared by dissolving monobasic potassium phosphate in 800 mL water, 4 mL of triethylamine was added and its pH was adjusted to 4.5 by phosphoric acid, and finally diluted to 1000 mL with water. The mobile phase was methanol/buffer solution at a ratio of 55:45, and the flow rate was 1 mL/min. An injection volume of 20 μL of the sample was injected through the column. The detection wavelength was 245 nm. Calibration curve was prepared over the concentration range of 0.2, 0.5, 1.0, 2.0, 5.0, 10.0, and 20.0 $\mu\text{g/mL}$ against the area under the curve.

2.3. Samples pretreatment for SR- μCT

Three tablets were sampled at predetermined time points of 1, 2, 4, 6, 8, 12, and 16 h from the dissolution medium to study the temporal changes in the microstructure of the bilayer osmotic pump tablets. Owing to the interference of the dissolution medium during the μCT scans for acquiring images, the samples were desiccated. Different methods of drying have been reported in the literature²⁵. In this experiment, the silica drying method was applied due to the minimal changes in the internal microstructure of the osmotic pump tablet. The tablets were placed in an airtight vessel containing dried silica for assisting rapid drying for 72 h to ensure they completely dried before the acquisition of the tomographic image.

To investigate microstructural detail directly of the tablet at different dissolution stages, wet dissolution conditioned tablet samples were also prepared. The samples at predetermined time

were taken out from the dissolution media and μCT was performed immediately.

2.4. Image acquisition by SR- μCT

SR- μCT tomographic images were acquired from the beam line BL13W1 at SSRF of the osmotic pump tablets. The tablets were scanned by the synchrotron radiation at the photon energy level of 18 keV, and X-ray window dimensions were maintained at 45 mm \times 5 mm for the exposure of rays to the tablets. The double-crystal monochromator with Si (111) and Si (311) crystals was used to monochromatize the X-rays. Synchrotron radiation source was placed at the distance of 34 cm from the sample and after penetrating through the sample the X-rays were converted to the visible light by using a cleaved Lu_2SiO_5 : Ce single crystal scintillator (10 μm thickness). The obtained projections were magnified by diffraction-limited microscope optics (1.25 \times) and digitized by high-resolution with an effective pixel size of 5.2 μm (ORCA Flash 4.0 Scientific CMOS, Hamamatsu K.K., Shizuoka Pref., Japan, physical pixel size: 6.5 μm). The exposure period was maintained for 0.8 s and the distance between the detector and the sample was set at 30 cm to obtain good phase contrast. For each sample, 1080 projection images were captured with an angular step size of 0.17° for 180° rotation. Flat-field (tomogram obtained without sample) and dark-field (tomogram obtained after shutting off the X-rays) images were collected during each acquisition procedure to correct the electronic noise and variations in the X-ray light source brightness³¹.

PITRE was used for the phase contrast extractions and quality enhancement of reconstructed slices. Filtered back projection algorithm was used for the reconstruction of projections by using PITRE software. *In situ* visualization of the tablet and different qualitative and quantitative parameters were analyzed by using commercial software like Image-Pro Plus, Image-Pro Premier 3D, and Amira.

2.5. Video actuation by the camera

Tablets were divided into 7 groups containing 3 tablets in each group. The dissolution test was carried out to each group using paddle with 50 rpm speed following USP dissolution test method. At the predetermined time (1, 2, 4, 6, 8, 12, and 16 h), tablets were taken out and placed in the petri dish contained dissolution medium. Then videos were captured by using a digital video camera (Microsoft LifeCam Studio™) for 5 min using a 140 mm \times 20 mm petri dish containing about 200 mL of dissolution medium at 37 °C. Then videos were forwarded by 20 \times to view the release pattern of the drugs from the orifice effectively.

3. Results and discussion

3.1. Structure characterization by the SR- μCT

The detailed *in situ* structures of the bilayer osmotic tablets are revealed as shown in Fig. 1, with the drug layer and push layer identified within the tablet. The crystals of NaCl were seen in the push layer for creating the osmotic pressure and facilitating water absorption. Definite arrangement of PEO as a swelling agent could be seen in drug layer and push layer. The diameter of the tapering

orifice in the surface coating was approximately 500 μm . Two types of coating layers were identified, with the inner layer as the semi-permeable membrane and the outer layer as a dense protective layer. The 3D microstructures within the tablet were revealed *via* tomographic images and utilized for comprehensive structural analysis.

3.2. *In vitro* drug release kinetics from bilayer osmotic pump tablet

The *in vitro* dissolution profile of the bilayer osmotic pump tablets at different periods is illustrated in Fig. 2A, indicating 3 kinetic phases of during the drug release process. At the initial stage, *i.e.*, lag stage (0–2 h), only small amount of the drug was released, then drug release progressively increased up to 12 h. After this period, the drug release rate dramatically decreased, indicating the end phase of drug release. More than 90% of the drug was released within 16 h. Typically, desiccated tablets at 6 h (Fig. 2A and B) show the different structural transformation from a sectioned axial view. The hollow space between two layers revealed that a swollen layer formed and subsequently dried out during the desiccation process. A “U” shaped morphological structure in the push layer after 4 h dissolution time indicated that the pressure applied to the drug layer is exerted from the peripheral extension of push layer. At the initial stage, during the lag period of release, water absorption inside the tablet took place. This resulted in the formation of gelatinized PEO. Low molecular weight PEO in the drug layer will dissolve quickly resulting in a drug suspension. The high molecular weight PEO present in the push layer swells when it absorbs water^{32,33} and the swollen gelatinized PEO in the push layer functions as a driving force for expelling the gelatinized PEO in the drug layer. The movement of push layer from the core region to the peripheral region of the tablet was visualized (from the axial slice of the tablet) representing the pushing route for drug release through the orifice. The water content and fluidity observed at the peripheral region of the tablet were high such that the push layer and drug layer in this region expanded rapidly and shifted towards the orifice for drug release. Pressure was generated from the push layer to the drug layer for drug release after 2 h. The release rate reduced after 12 h due to the maximum expansion of the push layer and reduced drug levels in the drug layer.

From Fig. 2B, salt crystals were also identified in the push layer of the tablet which would create an osmotic gradient for

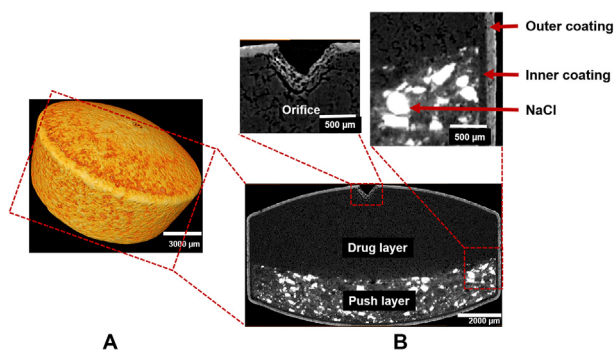


Figure 1 *In situ* structures of bilayer osmotic pump tablet as revealed by SR- μ CT. (A) 3D view of the tablet. (B) Orthoslice view of the tablet.

water penetration. From the visualization of push layer of the 6 h tablet, distinct regions can be described fined based on the salt crystal distribution. Spatial distribution of the crystals in the tablet was due to the shift of salt after dissolving. The dissolved salt preferentially moved to the outer peripheral region with the high the water content as compared to the core region, and also due to a high osmotic gradient. The outermost peripheral region consisted of the relatively larger dimension of recrystallized salt indicating the presence of concentrated solution, while that in the core regions were the same as that of the original tablet.

From this analysis of the images and release pattern, the observed release mechanism can be interpreted. The pushing force in the bilayer osmotic pump tablet initiated from the peripheral region of the tablet. With recrystallized salts concentrated in the peripheral region of the tablets, the consequence would be that the osmotic pressure within the push layer be greater in the peripheral region rather than from the core region.

3.3. Characterization of empty voids at different dissolution time points

To provide detailed 3D visualization of voids and vacant spaces within the tablets, photos were randomly segmented with different colors depending on the threshold difference of grey value as shown in Fig. 3. The vacant space was observed within the bilayer osmotic pump tablet indirectly, indicating the released drug layer portion. The vacant space created by the released portion of drug layer and drug release rate was highly correlated (Supporting Information Fig. S1), which is also in agreement with the study carried out in felodipine monolith osmotic pump tablets³⁰. Definite channels (typically at 4, 6, and 8 h) in the drug layer were observed indicating preferred routes for the drug release. From these observations, the drug release pathways and the release process can be understood and defined.

3.4. *In situ* visualization of channels during drug release

From the analysis of the voids within the tablet channel-like structures were identified in the drug layer. Also, at different dissolution times, well defined channels were observed through the semipermeable membrane. Through that channel, drug movement through these channels can be visualized (Fig. 4 and Supporting Information Movie). The channels were not identified after 1 and 2 h dissolution time, due to the overall swelling of the tablets or lag time for the formation of the channels. Distinct channels were visualized at 4 h. As the push layer of the tablets contained particles of red iron oxide, dark red color, minute traces are seen, indicating the release channels. The formation of distinct channels from the peripheral to the orifice of the tablets had revealed that the pressure in the osmotic pump tablets was generated through the peripheral region of the tablets together with channels formed from the peripheral due to excess pressure generated by the push layer at peripheral region. This finding supports the view that the pressure in the bilayer osmotic is initiated solution flow from the peripheral region of the tablets to the orifice of tablets. After 12 and 16 h, the drug layer was exhausted and only swollen push layer is present (Fig. 4). The drug release channels originating from the peripheral region of the tablets to the orifice indicated that a definite pathway was created for releasing the drug through the orifice.

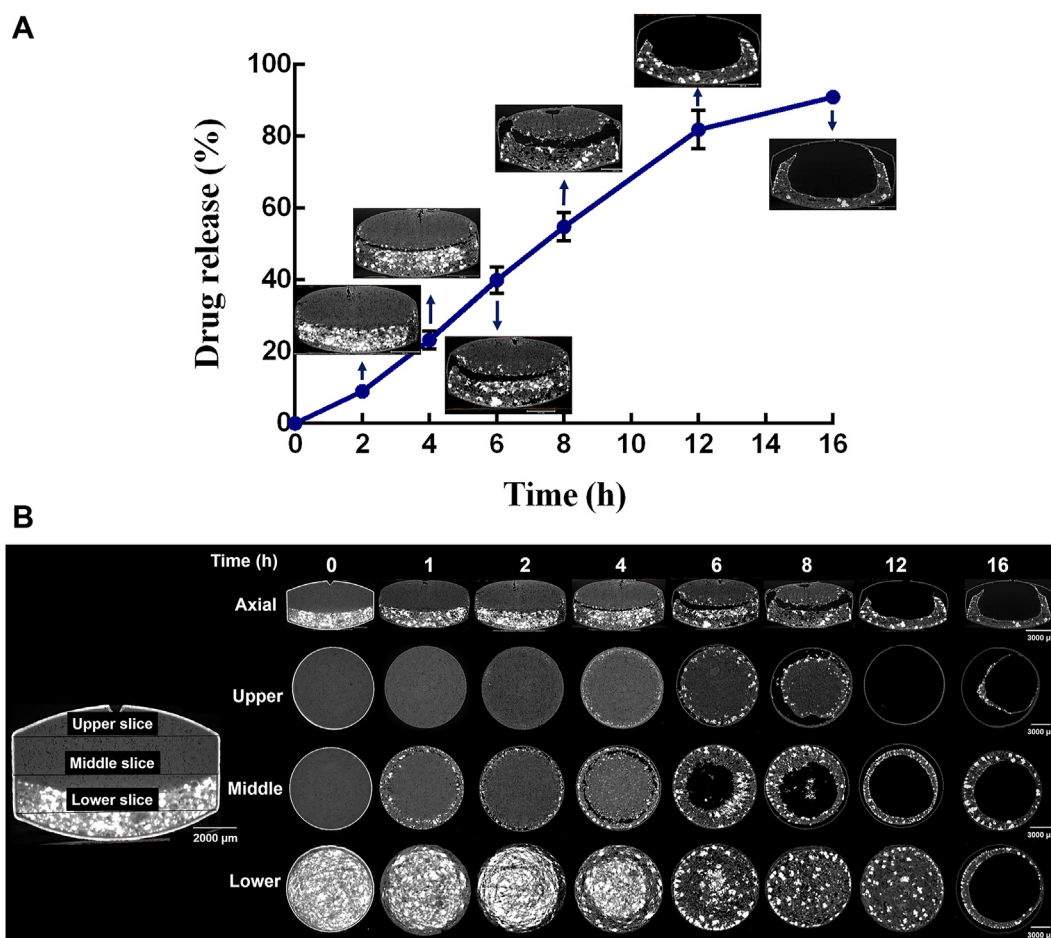


Figure 2 *In vitro* dissolution profile of bilayer osmotic pump tablet at different periods ($n = 6$ for the tablet of dissolution experiment). (A) Pictures represent the axial orthoslice at the respective dissolution time point. (B) Internal structure visualization of desiccated bilayer osmotic pump tablets at different dissolution time. Upper, middle, and lower represent the radial slice at the respective position.

3.5. *In situ* visualization of crystals inside the tablets

The pattern of NaCl crystal movement in the peripheral region of the tablet from the push layer to the drug layer is shown in

[Supporting Information Fig. S2](#). The peripheral upward movement of the salt from the push layer to the drug layer indicated that the osmotic pressure was developed peripherally. The vacant spaces at the center region of the desiccated tablet support the finding that

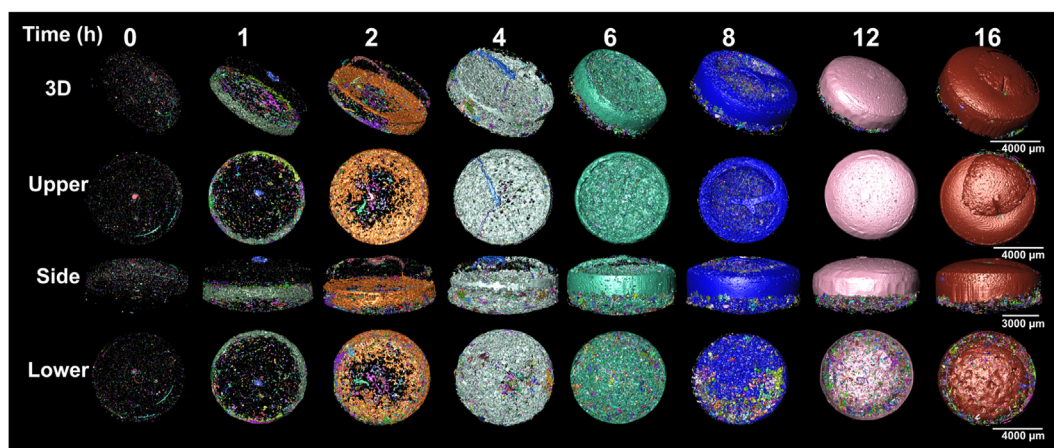


Figure 3 3D structures of extracted voids from desiccated tablet samples. The voids were randomly segmented with different colors, which represent the individual voids (The color is randomly selected by the software, and the voids are indicated by the colors ($n = 3$ for the tablet at each dissolution time point)).

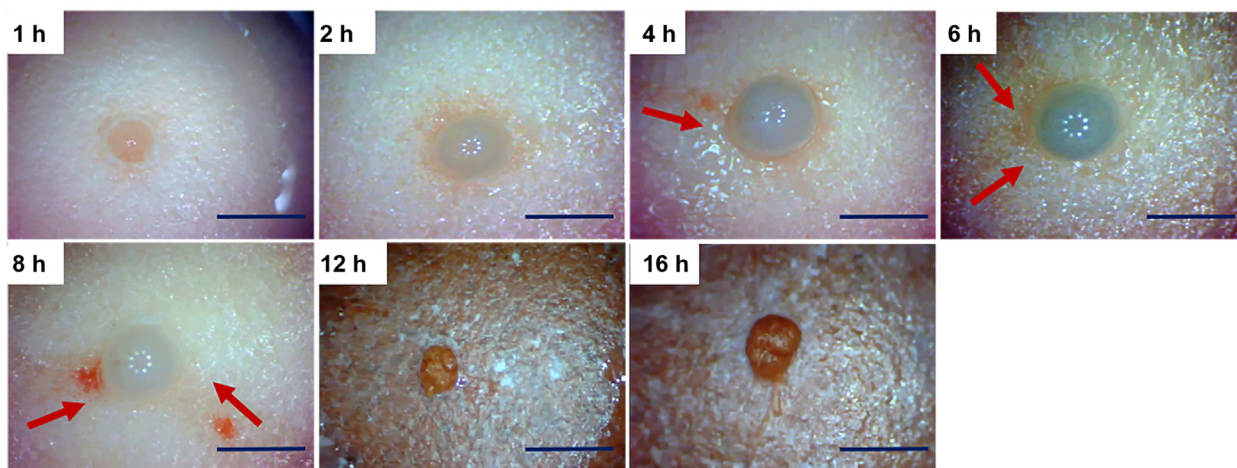


Figure 4 *In situ* visualization of tablets *via* a camera at different dissolution time. The arrows in the figure represent channels through which the drug was released. Drug layer was released till 8 h through definite channels. Reddish brown color after 12 h indicated that drug layer was exhausted and push layer was released. The scales in the figure represented 1 mm.

the push layer moved to the peripheral regions and subsequently to the drug layer.

The crystals were characterized by dividing the tablet into three regions, *viz.*, upper, middle, and lower region as shown in Fig. 5A. Each section was analyzed from the respective region with a height of 1.5 mm (289 pixels of slices), crystals were extracted by using Image-Pro Premier 3D software to reveal special distribution and visualization (Fig. 5B and C). A pattern of crystal movement from the push layer to the drug layer could be visualized with movement from the peripheral region indicating presence of more concentrated solution of NaCl for creating more push force to the drug layer as shown in Fig. 5C.

Relatively high amount of solution in the peripheral region resulted in rapid swelling and prompt movement of the push layer towards the drug layer. When salts at the push layer in the peripheral region dissolved, they created a more osmotic pressure gradient, attracting more dissolution fluid inside the tablets that resulted in swelling of PEO. As compared to the outer peripheral region, the inner region had less water content that resulted into the formation of a higher concentration salt solution, which progressively diffused towards the outer peripheral region. Subsequently, this region moved towards the drug layer due to high fluidity thus creating osmotic upsurge for drug layer release. When the tablet was dried, the salts recrystallized according to their distribution in the dissolution conditioned state. This spatial distribution of the crystals in the peripheral region in the osmotic push layer and their movement pattern indicated that osmotic push force was created from the peripheral region of the tablets.

3.6. Study of dissolution conditioned PPOP tablets

The dissolution conditioned samples were visualized *via* SR- μ CT in an attempt to define the exact microstructural transformations at different dissolution times. Due to the presence of dissolution media within the tablet and its interference with the synchrotron X-ray absorption, the quality of the image obtained was not in an optimum state. However, different transformation states were visualized to understand the drug release mechanism.

The typical release state from the bilayer osmotic pump tablet at 6 h is shown in Fig. 6A. The gap between two layers of the tablet identified in the desiccated tablet was not seen. On the contrary, a swollen state region inside the tablet is identified. Three regions in the push layer were distinguished as an osmotic front, infiltration state, and dormant state which had functionally different attributes. However, in the case of drug layer, only two regions namely, the osmotic region and dormant region could be visualized.

The osmotic front was characterized by high fluidity and mobility which consisted of dissolved salt and PEO for creating the osmotic push force to the drug layer. In the drug layer, an osmotic front was formed beneath the semipermeable membrane and also between two layers of the tablet. The infiltration region was characterized by the less compacted mass of PEO beneath the osmotic front of the push layer. A “bubble like” spherical structure was visualized in this region (Supporting Information Fig. S3). Bubbles formed during the swelling of high molecular weight PEO in the push layer. The infiltration region was also characterized by low salt concentration (comparatively low brightness in images) as salt from this region moved to the osmotic front. In the dormant region, water had not penetrated and it remained in its original state.

The mass movement and the osmotic pressure gradient in the osmotic front were high due to the presence of more fluid, dissolved NaCl, and PEO. There was a continuous tendency to draw water into this region that resulted in swelling. High molecular weight PEO in the push layer resulted in a high swelling index which created a higher osmotic push force from the osmotic front. A series of transformation states from the dormant region to infiltration region and finally to the osmotic front is visualized at 6 h dissolution time as shown in Fig. 6A. The dormant region progressively decreased its size and finally disappeared after 8 h dissolution time as shown in Fig. 6B. Similarly, the osmotic front increased its dimension showing the swollen state of PEO.

Functionally different intermediate states within osmotic bilayer tablets provide insight into the drug release mechanism. Movement of the osmotic front towards the drug layer through the peripheral region indicated that the pushing upsurge force was created through the peripheral push region. Less compacted mass

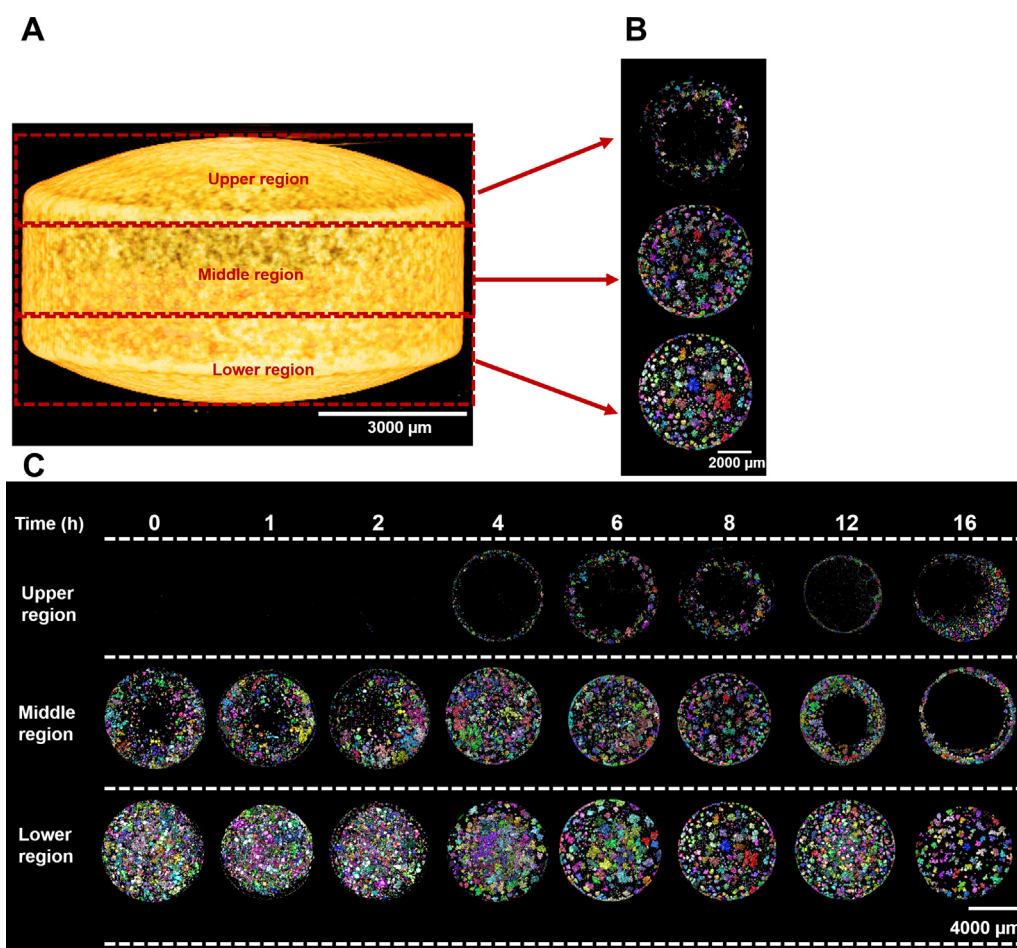


Figure 5 Spatial distribution of NaCl crystals in different regions within desiccated bilayer osmotic pump tablets during the drug release process. (A) Division of the tablet into 3 regions. (B) Upper, middle, and lower regions of segmented extracted crystals. (C) Extracted crystals at different dissolution times. Different colors represent a specific single crystal ($n = 3$ for the tablet at each dissolution time point).

in the infiltration region indicated that PEO from the infiltration region moved to the osmotic front region, where swelling took place and the push force was created. The dormant region slowly converted to the infiltration region and osmotic front to create pressure on the drug layer. The drug layer also absorbed the dissolution fluid that resulted in an increase in the fluidity of this region. As the push layer triggered the pushing action through the peripheral region, the drug layer moved through the same route towards the orifice to create controlled drug delivery.

3.7. Subterranean river model over the traditional push–pull model

The push–pull theory³ was postulated based on the osmotic phenomenon without taking into account *in situ* formed 3D structures within the tablets. The theory is briefly explained as follow; when the bilayer tablet was placed in the dissolution media, the media penetrated in both layers of the bilayer osmotic tablet leading to the formation of the suspension in the drug layer which is referred to the pull layer. The formed suspension from this layer will be released through the orifice when the push layer, having a high expandable function, expands in volume after the dissolution media absorbed in this layer^{34,35}.

From the 3D observation of the bilayer osmotic pump tablet, complex phenomena within the bilayer osmotic pump tablet

during the drug release process were identified with a number of different structures present within the tablet during the drug release process. The 3D view of a desiccated osmotic pump tablet revealed that a larger portion of the push layer structure was located in the upper region of the tablet having moved *via* the peripheral pathway as illustrated in Fig. 2B. The core region of the push layer translocated towards the peripheral region of the tablet due to high fluidity at the periphery during the release process. From the dissolution conditioned tablet visualization, movement of the osmotic front from the push layer to the drug layer was visualized. The loose swollen infiltration region and the dormant region beneath the osmotic front were shown in push layer at different states of expansion as shown in Fig. 6. According to these 3D observations, it is clear that the osmotic front pushed the suspension formed in the drug layer towards the orifice at a relatively higher rate compared to the infiltration region and dormant region through the peripheral routes. The release mechanism can be described as a ‘Subterranean river model’ to represent an understanding of the drug release mechanism from the bilayer osmotic pump tablets as illustrated in Fig. 7.

During drug dissolution and with the underground river flowing, no morphological changes are seen externally. However, under the surface and layers, the current of water would be flowing in different layers, as revealed by this study. The water taken up by the tablet primarily moved from the upper layer, even

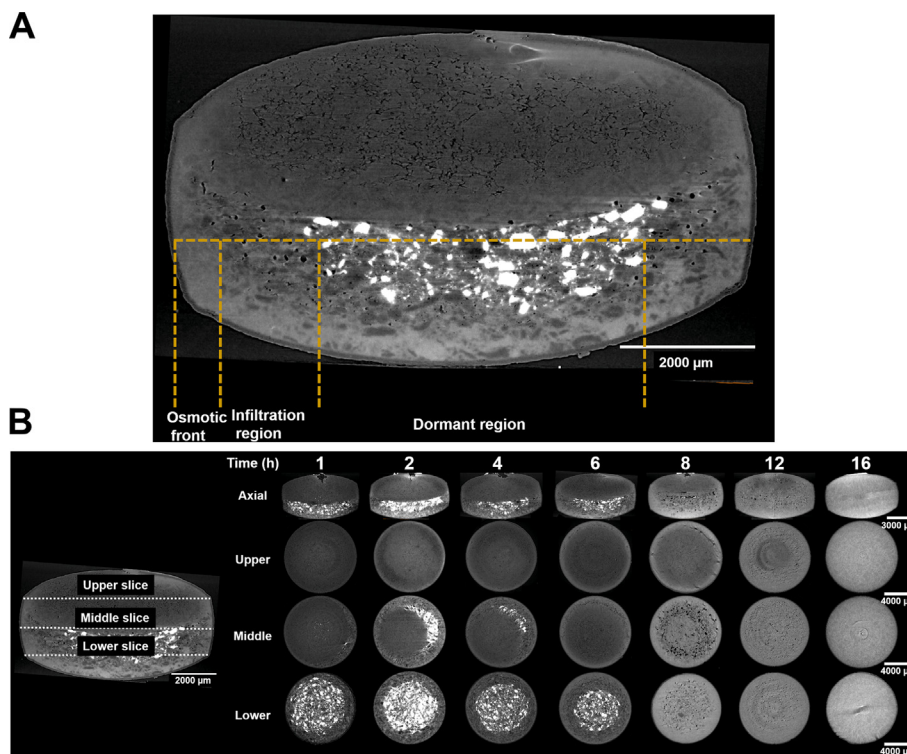


Figure 6 *In situ* view of dissolution conditioned wet bilayer tablets at different dissolution time. (A) Representation of different regions (osmotic front, infiltration state, and dormant state) in the tablet at 6 h by axial orthoslice. White color represents high-density material (NaCl). (B) Representation of internal structure of the bilayer osmotic pump tablet at different dissolution time points.

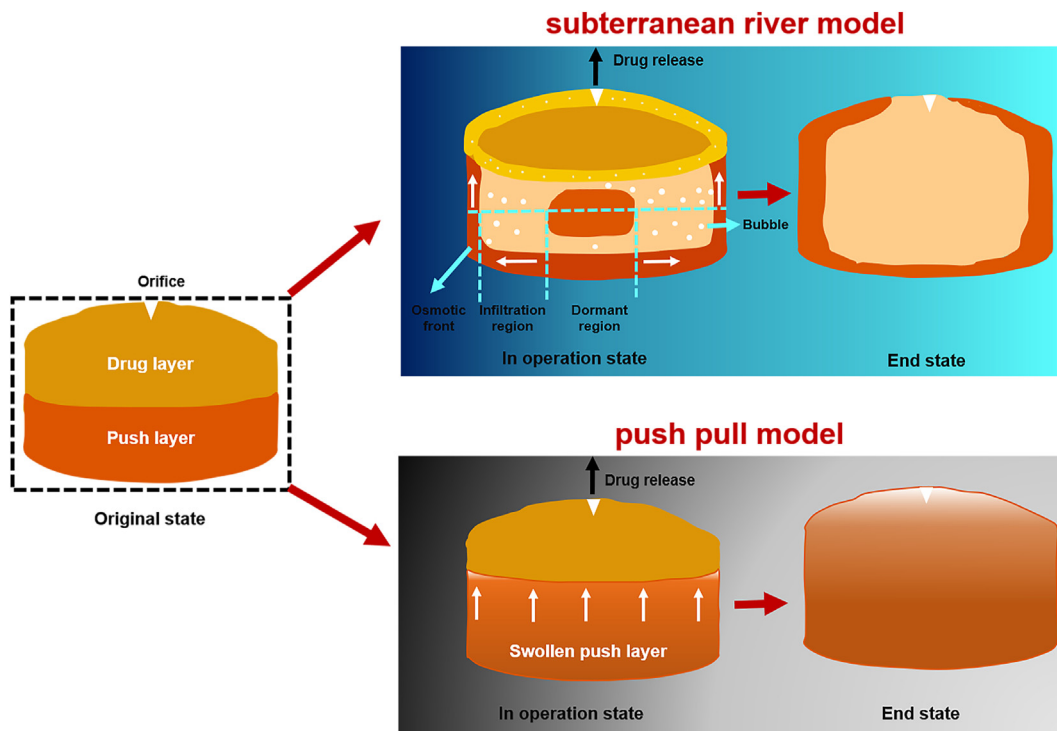


Figure 7 A schematic model for the release kinetics from bilayer osmotic pump tablets over the traditional push–pull model.

though it appeared to move in an integrated manner from all the regions of the layers. The flowrate of water in subterranean river below the upper layer was low and, at the inner side, did not appear to move at all due to resistance force created *via* viscosity. In the same manner, the push layer seemed to move to the drug layer in an integrated manner but in reality, it moved by creating different push layers in the bilayer osmotic pump tablet.

4. Conclusions

Bilayer osmotic pump tablets were investigated for comprehensive analysis of 3D microstructural transformations at different dissolution time using SR- μ CT. By the application of various imaging algorithms, microstructural transformations including crystal movement pathways, voids, and channel pathways were characterized. Comprehensive analysis of *in situ* formed 3D structures and their retrospective analysis gave direct understanding about the drug release mechanism from the tablet. Osmotic push force was more pronounced at the periphery region of the tablets as high crystal concentrations accumulated at the site. Definite channels, originating in the peripheral region to the orifice indicated the pathways for drug movement to the orifice. *In situ* formed functionally different intermediate states during drug dissolution of wet tablet have been identified providing insight that the osmotic push force was primarily due to the osmotic front at the peripheral region. A subterranean river model for the drug release kinetics from bilayer osmotic pump is proposed, taking into account the several microstructural transformations identified from a 3D structural view over push-pull model. This study focuses on *in situ* formed 3D structures and their transformation to unveil the concealed release mechanism, opening a new door in the pharmaceuticals arena.

Acknowledgements

The authors are grateful for the National Nature Science Foundation of China (Nos. 81803446, 81803441 and 81773645), Key Program for International Science and Technology Cooperation Projects of China (2020YFE0201700), and the Youth Innovation Promotion Association of CAS (2018323). Thanks also go to the staff from Shanghai Synchrotron Radiation Facility for the assistance during the experiment and data collection.

Author contributions

Abi Maharjan and Hongyu Sun performed research and equally contributed to this research. Li Wu, Jiwen Zhang and Xianzhen Yin designed research. Tiqiao Xiao, Guanyun Peng and Ke Li collected data. Zeying Cao and Jun Liu contributed in preparation of manuscript. Junqiu Ji, Peter York and Balmukunda Regmi contributed in preparation of manuscript and guided during research. All authors have read and approved the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supporting information

Supporting data to this article can be found online at <https://doi.org/10.1016/j.apsb.2021.11.008>.

References

- Ahmed K, Shoaib MH, Yousuf RI, Siddiqui F, Qazi F, Iftikhar J, et al. Comparative pharmacokinetics of osmotic-controlled and immediate-release eperisone tablet formulation in healthy human subjects using a sensitive plasma LC-ESI-MS/MS method. *Sci Rep* 2020;**10**:1867.
- Thakkar HP, Pancholi N, Patel CV. Development and evaluation of a once-daily controlled porosity osmotic pump of tapentadol hydrochloride. *AAPS J* 2016;**17**:1248–60.
- Verma RK, Krishna DM, Garg S. Formulation aspects in the development of osmotically controlled oral drug delivery systems. *J Control Release* 2002;**79**:7–27.
- Eckenhoff B, Yum SI. The osmotic pump: novel research tool for optimizing drug regimens. *J Biomater* 1981;**2**:89–97.
- Sandberg A, Ragnarsson G, Jonsson UE, Sjogren J. Design of a new multiple-unit controlled-release formulation of metoprolol-metoprolol CR. *Eur J Clin Pharmacol* 1988;**33**:S3–7.
- Daniel BS, Niels B, Ture KL. Egalet® , a novel controlled release system. *Ann N Y Acad Sci* 1991;**618**:578–80.
- Mandal AS, Biswas N, Karim KM, Guha A, Chatterjee S, Behera M, et al. Drug delivery system based on chronobiology—a review. *J Control Release* 2010;**147**:314–25.
- Santus G, Baker RW. Osmotic drug-delivery—a review of the patent literature. *J Control Release* 1995;**35**:1–21.
- Malaterre V, Ogorka J, Loggia N, Gurny R. Oral osmotically driven systems: 30 years of development and clinical use. *Eur J Pharm Biopharm* 2009;**73**:311–23.
- Kumar P, Singh S, Mishra B. Development and evaluation of elementary osmotic pump of highly water soluble drug: tramadol hydrochloride. *Curr Drug Deliv* 2009;**6**:130–9.
- Emara LH, Taha NF, El-Ashrawy AA, Raslan HM, Mursi NM. Controlled porosity osmotic pump system for the delivery of diclofenac sodium: *in-vitro* and *in-vivo* evaluation. *Pharm Dev Technol* 2014;**19**:681–91.
- Liu L, Ku J, Khang G, Lee B, Rhee JM, Lee HB. Nifedipine controlled delivery by sandwiched osmotic tablet system. *J Control Release* 2000;**68**:145–56.
- Thombre AG, Cardinal JR, DeNoto AR, Gibbes DC. Asymmetric membrane capsules for osmotic drug delivery II. *In vitro* and *in vivo* drug release performance. *J Control Release* 1999;**57**:65–73.
- Waterman KC, Goeken GS, Konagurthu S, Likar MD, MacDonald BC, Mahajan N, et al. Osmotic capsules: a universal oral, controlled-release drug delivery dosage form. *J Control Release* 2011;**152**:264–9.
- Wu C, Zhao ZZ, Zhao Y, Hao YN, Liu Y, Liu C. Preparation of a push-pull osmotic pump of felodipine solubilized by mesoporous silica nanoparticles with a core-shell structure. *Int J Pharm* 2014;**475**:298–305.
- Zhang ZH, Dong HY, Peng B, Liu HF, Li CL, Liang M, et al. Design of an expert system for the development and formulation of push-pull osmotic pump tablets containing poorly water-soluble drugs. *Int J Pharm* 2011;**410**:41–7.
- Malaterre V, Ogorka J, Loggia N, Gurny R. Approach to design push-pull osmotic pumps. *Int J Pharm* 2009;**376**:56–62.
- Wang Y, Wertheim DF, Jones AS, Coombes AG. Micro-CT in drug delivery. *Eur J Pharm Biopharm* 2010;**74**:41–9.
- Richardson JC, Bowtell RW, Mader K, Melia CD. Pharmaceutical applications of magnetic resonance imaging (MRI). *Adv Drug Deliv Rev* 2005;**57**:1191–209.
- Markl D, Wang P, Ridgway C, Karttunen AP, Chakraborty M, Bawuah P, et al. Characterization of the pore structure of functionalized calcium carbonate tablets by terahertz time-domain spectroscopy and X-ray computed microtomography. *J Pharm Sci* 2017;**106**:1586–95.
- Kandpal LM, Cho B-K, Tewari J, Gopinathan N. Raman spectral imaging technique for API detection in pharmaceutical microtablets. *Sens Actuators B Chem* 2018;**260**:213–22.

22. Yin XZ, Wu L, Li Y, Guo T, Li HY, Xiao TQ, et al. Visualization and quantification of deformation behavior of clopidogrel bisulfate polymorphs during tableting. *Sci Rep* 2016;**6**:21770.
23. Yin XZ, Li HY, Guo Z, Wu L, Chen FW, de Matas M, et al. Quantification of swelling and erosion in the controlled release of a poorly water-soluble drug using synchrotron X-ray computed microtomography. *AAPS J* 2013;**15**:1025–34.
24. Wu L, Wang LB, Wang SX, Xiao TQ, Chen M, Shao Q, et al. Three dimensional structural insight of laser drilled orifices in osmotic pump tablets. *Eur J Pharm Sci* 2016;**93**:287–94.
25. Yin XZ, Li HY, Liu RH, Chen J, Ji JQ, Chen J, et al. Fractal structure determines controlled release kinetics of monolithic osmotic pump tablets. *J Pharm Pharmacol* 2013;**65**:953–9.
26. Zhang L, Wu L, Wang CF, Zhang GQ, Yu L, Li HY, et al. Synchrotron radiation microcomputed tomography guided chromatographic analysis for displaying the material distribution in tablets. *Anal Chem* 2018;**90**:3238–44.
27. Fang LW, Yin XZ, Wu L, He YP, He YZ, Qin W, et al. Classification of microcrystalline celluloses via structures of individual particles measured by synchrotron radiation X-ray micro-computed tomography. *Int J Pharm* 2017;**531**:658–67.
28. Xu HM, Li Z, Pan H, Zhang ZH, Liu DD, Tian BC, et al. A novel bilayer ascending release osmotic pump tablet: *in vitro* investigation and *in vivo* investigation in pharmacokinetic study and IVIVC evaluation. *Int J Pharm* 2013;**458**:181–7.
29. Malaterre V, Metz H, Ogorka J, Gurny R, Loggia N, Mader K. Benchtop-magnetic resonance imaging (BT-MRI) characterization of push–pull osmotic controlled release systems. *J Control Release* 2009;**133**:31–6.
30. Li HY, Yin XZ, Ji JQ, Sun LX, Shao Q, York P, et al. Microstructural investigation to the controlled release kinetics of monolith osmotic pump tablets via synchrotron radiation X-ray microtomography. *Int J Pharm* 2012;**427**:270–5.
31. Sun X, Wu L, Maharjan A, Sun HY, Hu XX, York P, et al. Static and dynamic structural features of single pellets determine the release behaviors of metoprolol succinate sustained-release tablets. *Eur J Pharm Sci* 2020;**149**:105324.
32. Nakajima T, Takeuchi I, Ohshima H, Terada H, Makino K. Push–Pull controlled drug release systems: effect of molecular weight of polyethylene oxide on drug release. *J Pharm Sci* 2018;**107**:1896–902.
33. Apicella A, Cappello B, Del Nobile MA, La Rotonda MI, Mensitieri G, Nicolais L. Poly(ethylene oxide) (PEO) and different molecular weight PEO blends monolithic devices for drug release. *J Biomater* 1993;**14**:83–90.
34. Malaterre V, Ogorka J, Loggia N, Gurny R. Evaluation of the tablet core factors influencing the release kinetics and the loadability of push–pull osmotic systems. *Drug Dev Ind Pharm* 2009;**35**:433–9.
35. Swanson DR, Barclay BL, Wong PSL, Theeuwes F. Nifedipine gastrointestinal therapeutics system. *Am J Med* 1987;**83**:1–9.