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Micro-computed tomography and brightness-mode ultrasound show air entrapments inside tablets

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Abstract: Controlled disintegration of pharmaceutical tablets has been of interest for consistency checks and drug delivery. Under sonication, tablet disintegration is accelerated. This acceleration has been attributed to the existence of microscopic air pockets inside compacted tablets. In this study, we investigated the existence of such pockets by subjecting tablets to micro-computed tomography. In addition, we subjected tablets from the same batch to sonography. The tablets were measured to have an ultrasonic swelling rate of $162\pm16\,\mu\mathrm{m\,s^{-1}}$. The micro-computed tomography images showed air pockets of up to $9\,\mu$m in diameter, some of which were visibly connected to each other. The brightness-mode images showed scattering from inside the tablets, suggesting cavitation activity. We conclude that, inside the tablets investigated, microscopic air entrapments exist, whose pulsations are detectable with brightness-mode ultrasound.

Keywords: μCT, B-mode, air pockets, scattering, tablet swelling, tablet disintegration.

1 Introduction

Purposeful slow disintegration of pharmaceutical tablets has been of interest for consistency checks in industry and for controlled drug release *in vivo* [1–4]. Subjecting tablets to low-amplitude ultrasound has been known to speed up the disintegration process [4–7]. This speeding up has been attributed to friction caused by pulsating microscopic air entrapments under sonication [5, 6]. The pulsating behaviour of solid-encapsulated gas spheres has been derived and simulated previously [8]. The theoretical scattering response of microscopic pockets increases with size [9]. With the aide of high-speed photography during sonication, such pulsating air pockets had been observed on the surface of pre-disintegrated tablet fragments [6]. Nevertheless, the existence of air pockets inside undamaged tablets had not been proven.

For uncoated and film-coated tablets, tablet swelling is regarded as the first stage of disintegration [7]. In a recent study, the swelling rate of otherwise identical tablets was found to differ between production batches, but was found to match for the same production batch [7].

The purpose of this study was to tomographically image tablets prior to their disintegration. The swelling rate was subsequently determined from brightness-mode ultrasonic imaging. Although a multitude of tomographic imaging technologies exist, our method of choice required a three-dimensional representation, near-μm resolution, unchanged material integrity, and the ability to differentiate between gaseous and solid materials. Our method of choice, micro-computed tomography (μCT) is known for its resolution [10, 11]. It has been used to image three-dimensional porous structures [12, 13].

2 Materials and methods

2.1 Micro-computed tomography

A $31.9\times31.9\times81.6$-mm^3 scaffold was created from acrylonitrile butadiene styrene cuboids. The scaffold contained six compartments of equal height, separated in z-direction. Four Panadol 500 mg film-coated $17.2\times7.9\times5.9$-mm^3 ellipsoid analgesia tablets (GlaxoSmithKline Consumer Healthcare A/S, Brøndby, Denmark) were placed each in a separate compartment. Calibration materials were placed in the two bottom compartments.

The scaffold was positioned on a rotating plate inside the imaging chamber inside a MicroXCT-400 device (Carl Zeiss AG, Oberkochen, Germany). Tomographic imaging was done using using the procedure previously published [14]. The X-ray source operated at a 10-W power and an 80-kV peak voltage. The exposure time was 5 s per image. A detection scintil-

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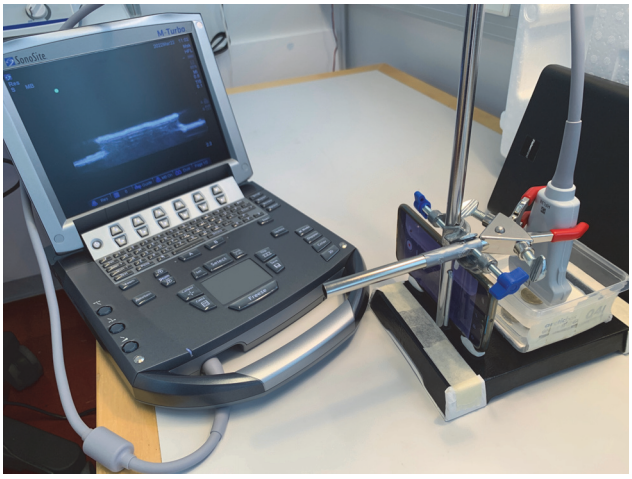

Fig. 1: Photographic overview of the disintegration setup. An ultrasound probe was clamped facing downward towards a nickel-brass 1-SHP reflector inside a water-filled container. A cellphone positioned on the clamp stand was used for capturing continuous video footage.

lator with a 10× objective was used. After each image, the plate automatically rotated to a different position. In total, 1601 projections were acquired, evenly distributed over 360°. The resulting voxel size corresponded to $2\times2\times2\,\mu\text{m}^3$.

To create three-dimensional images from the μCT data, the data were reconstructed by XMRe-constructor 8.1.6599 software (Zeiss). Avizo 2020.2 software (Thermo Fisher Scientific, Waltham, MA, USA) was used for digital cutting and morphometric evaluation. The resulting three-dimensional images were freely manipulated and digitally cut back into slices for viewing and for precise morphometric measurements. Cross-section images were converted to negative and subjected to a 0.8 segmentation threshold using MATLAB® (The MathWorks, Inc., Natick, MA, USA). The original greyscale image was then overlain by the thresholded binary image in red.

In parallel with μCT imaging, tablets from the same batch were subjected to sonic disintegration.

2.2 Disintegration setup

An experimental setup to monitor tablet disintegration, similar but not identical to the experimental setup used for production batch testing [7], is shown in Figure 1. It comprised a 1220 Arctic box container (Plast 1 A/S, Hørsholm, Denmark) of $115\times115\times55$-mm^3 outer dimensions, placed on the base of a clamp stand. A P30 lite cellphone (Huawei Technologies Co., Ltd., Shenzhen, P.R. China), recording continuously throughout the experiments, was positioned in landscape orientation on the clamp stand using Bostik Prestik (Permoseal (Pty) Ltd, Montague Gardens, South Africa) reusable putty adhesive. A nickel-brass 1-SHP reflector was attached to the bottom of the container using Bostik Prestik.

The HFL38x 13–6-MHz linear probe of a SonoSite® M-Turbo® sonography device (FUJIFILM Sonosite, Inc., Bothell, WA, USA) was clamped 14 mm above the reflector, such that its primary propagation direction was perpendicular to the reflector surface.

The sonography device was operating in musculoskeletal pulsed brightness mode with a penetration depth of 22 mm relative to the probe surface. Ultrasound pulses were indicated to have a mechanical index of 0.8 and a thermal index of 0.1. The machine settings remained unaltered throughout the experiments. During controls, the ultrasound machine was switched off without altering the position of the probe.

The experimental procedure was as follows. Before each experiment, the container was freshly filled with degassed Hervanta tap water, whose temperature was measured to be 19°C in each experiment. A Panadol tablet was placed manually on the reflector. The moment of manual release, captured by the cellphone, was regarded as $t = 0$. The effect of sonication during swelling was considered gone in 60 s.

All brightness-mode video clips, recorded at 7.5 frames per second, were converted to still frames. A total number of 9450 frames was processed using MATLAB®. The frames were cropped to the 60 centre-most imaging lines relative to the tablet. For each imaging line in each brightness-mode image, the instantaneous perceived tablet swelling was determined by automatically selecting the proximal peak amplitude and marking the corresponding perceived distance r' to the tablet surface. The perceived swelling rate $\dot{r}'$ of a tablet was computed by least-squares fitting of a line $f(t) = \text{constant} - \dot{r}'t$ through all points (t, r') on the interval $t \in [0, 26]$ s. This perceived swelling rate was subsequently converted to actual swelling rate $\dot{r}$ by multiplication by the ratio of the speeds of sound of the medium and the machine-assumed value thereof.

Twenty-one tablets from the same production batch were subjected to sonic disintegration. Video recordings were captured during the disintegration process.

3 Results and discussion

Figure 2 demonstrates a tomographic μCT image with a three-dimensional representation of a tablet cross-section and close-ups thereof. Microscopic cavities up to 9 μm in diameter could be appreciated in the close-up images. Moreover, some micro-cavities observed in the tablet were visibly connected to each other, as hypothesised.

Knowing the theoretical and empirical relation between scatterer size and backscattering response, it may be presumed

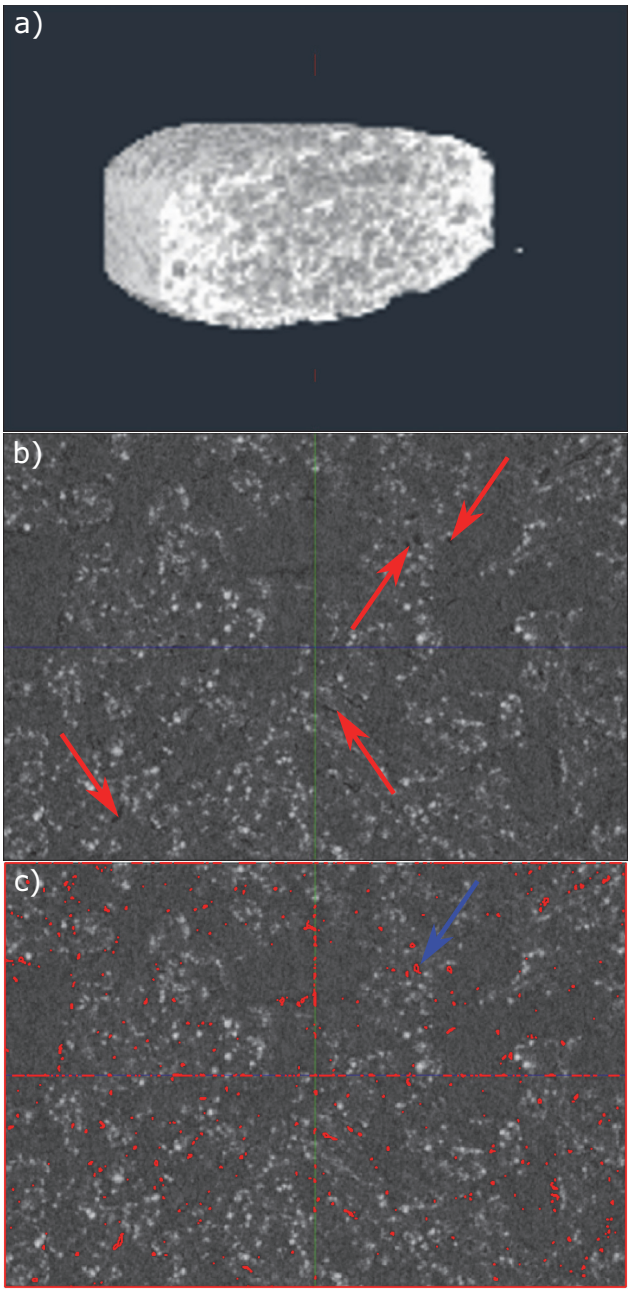

Fig. 2: Tomographic μCT image showing a three-dimensional representation of a tablet cross-section (a), a close-up of the cross-section (b), and the same close-up overlain by a thresholded binary (c). Air pockets are represented by dark grey (b) or red (c). Some large cavities have been marked by red arrows (b). An air pocket of 9-μm diameter has been marked by a blue arrow (c). Frames (b) and (c) correspond to 1.6$\times$1.1-mm^2 areas.

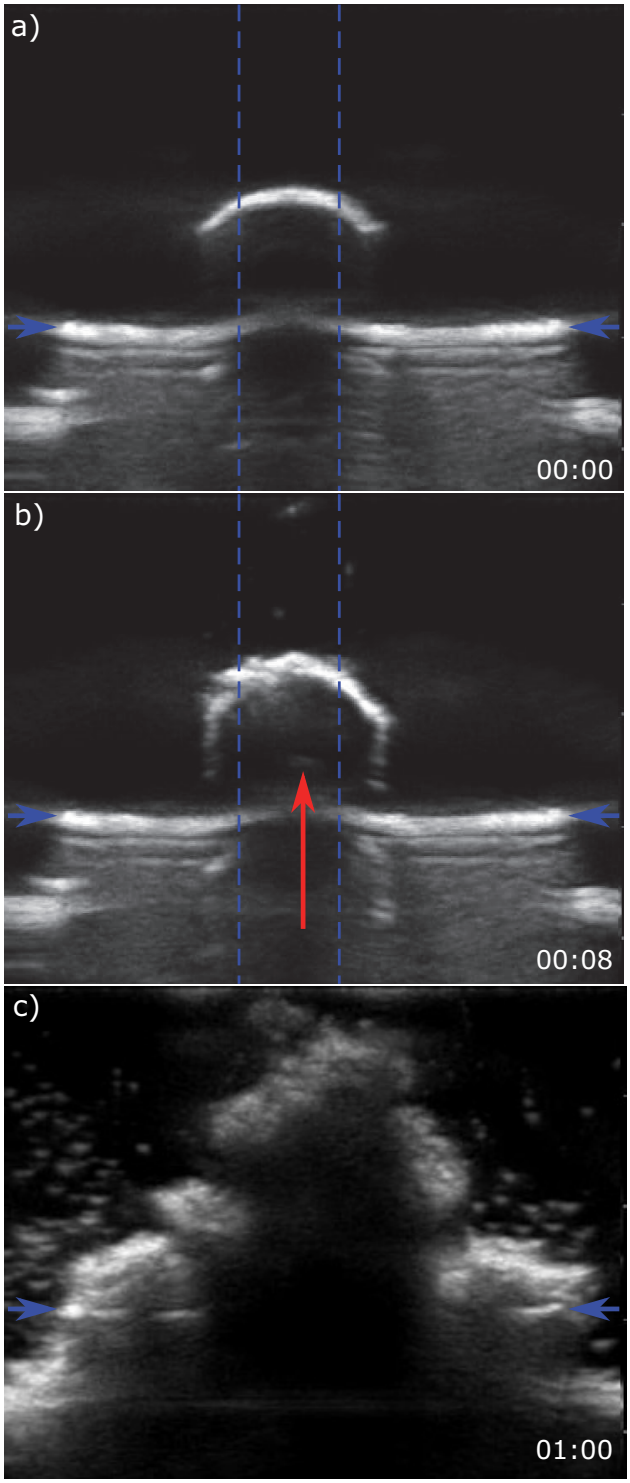

Fig. 3: Brightness-mode image of a tablet directly after placement on a visible reflector (a), after 8-s sonication (b), and after 60-s sonication (c). The direction of primary field propagation is from top to bottom. The 60-line region of interest has been marked by blue dashed lines. Suspected cavitation activity has been marked by a red arrow. The surface of the reflector has been indicated by blue arrows.

that some of the larger or connected microcavities observed with μCT are the strongest acoustic scatterers.

Figure 3 shows a typical example of strong scattering inside a tablet from the same batch. The frame directly after placement shows a strong reflection from the tablet surface and from the reflector. The frame taken after 8 s shows a sudden strong scattering response, that had disappeared in the next frame (not shown). We associate this transient scattering activity to cavitation-related behaviour. In addition, tablet fragments were observed breaking off and floating towards the probe surface. The lower-than-water density of these fragments and their strong scattering indicates gas presence inside these tablet fragments. After 60 s, the tablet was observed to have disintegrated and avalanched over the reflector surface, whose surface was still visible. The brightness-mode image showed superficial reflections from the disintegrated tablet, but no major acoustic activity inside the disintegrated tablet. We presume that any cavitation activity had ceased by that time.

From the brightness-mode data, the swelling rate was determined to be $162 \pm 16\,\mu\mathrm{m\,s^{-1}}$. The low standard deviations within the batch confirmed earlier findings. Furthermore, this finding justifies the use of different tablets from the same batch in this investigation.

4 Conclusion

Microscopic air entrapments exist inside the tablets studied. We may assume that these entrapments are causing the pulsations that have been detected with brightness-mode ultrasound.

Author statement

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