



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

Craig Stuart Carlson, Markus Hannula, Michiel Postema

### ► To cite this version:

Craig Stuart Carlson, Markus Hannula, Michiel Postema. Micro-computed tomography and brightness-mode ultrasound show air entrapments inside tablets. Current Directions in Biomedical Engineering, 2022, Proceedings of the 2022 Joint Annual Conference of the Austrian (ÖGBMT), German (VDE DGBMT) and Swiss (SSBE) Societies for Biomedical Engineering, 8 (2), pp.41-44. 10.1515/cdbme-2022-1012 . hal-03696315

**HAL Id: hal-03696315**

**<https://hal.science/hal-03696315>**

Submitted on 2 Sep 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

Craig S. Carlson\*, Markus Hannula, and Michiel Postema

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

<https://doi.org/10.1515/cdbme-2022-1012>

**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  $162 \pm 16 \mu\text{m s}^{-1}$ . The micro-computed tomography images showed air pockets of up to  $9 \mu\text{m}$  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:**  $\mu\text{CT}$ , 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 sim-

ulated 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- $\mu\text{m}$  resolution, unchanged material integrity, and the ability to differentiate between gaseous and solid materials. Our method of choice, micro-computed tomography ( $\mu\text{CT}$ ) 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

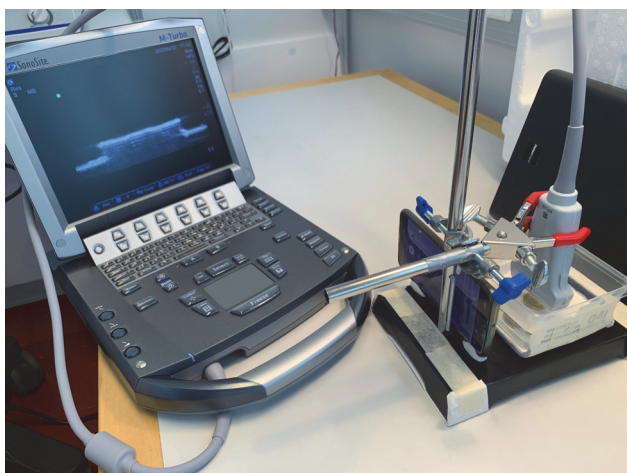
A  $31.9 \times 31.9 \times 81.6\text{-mm}^3$  scaffold was created from acrylonitrile butadiene styrene cuboids. The scaffold contained six compartments of equal height, separated in *z*-direction. Four Panadol 500 mg film-coated  $17.2 \times 7.9 \times 5.9\text{-mm}^3$  ellipsoid analgesia tablets (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 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-

\*Corresponding author: Craig S. Carlson, BioMediTech, Faculty of Medicine and Health Technology, Tampere University, Korkeakoulunkatu 3, 33720 Tampere, Finland and School of Electrical and Information Engineering, University of the Witwatersrand, Johannesburg, 1 Jan Smutsaan, Braamfontein 2050, South Africa, e-mail: [craig.carlson@tuni.fi](mailto:craig.carlson@tuni.fi)

Markus Hannula, BioMediTech, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland

Michiel Postema, BioMediTech, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland and School of Electrical Engineering, University of the Witwatersrand, Johannesburg, Braamfontein, South Africa



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

To create three-dimensional images from the  $\mu$ CT data, the data were reconstructed by XMRe-creator 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<sup>®</sup> (The MathWorks, Inc., Natick, MA, USA). The original greyscale image was then overlain by the thresholded binary image in red.

In parallel with  $\mu$ CT 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  $115\times 115\times 55\text{-mm}^3$  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<sup>®</sup> M-Turbo<sup>®</sup> 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  $19^\circ\text{C}$  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.

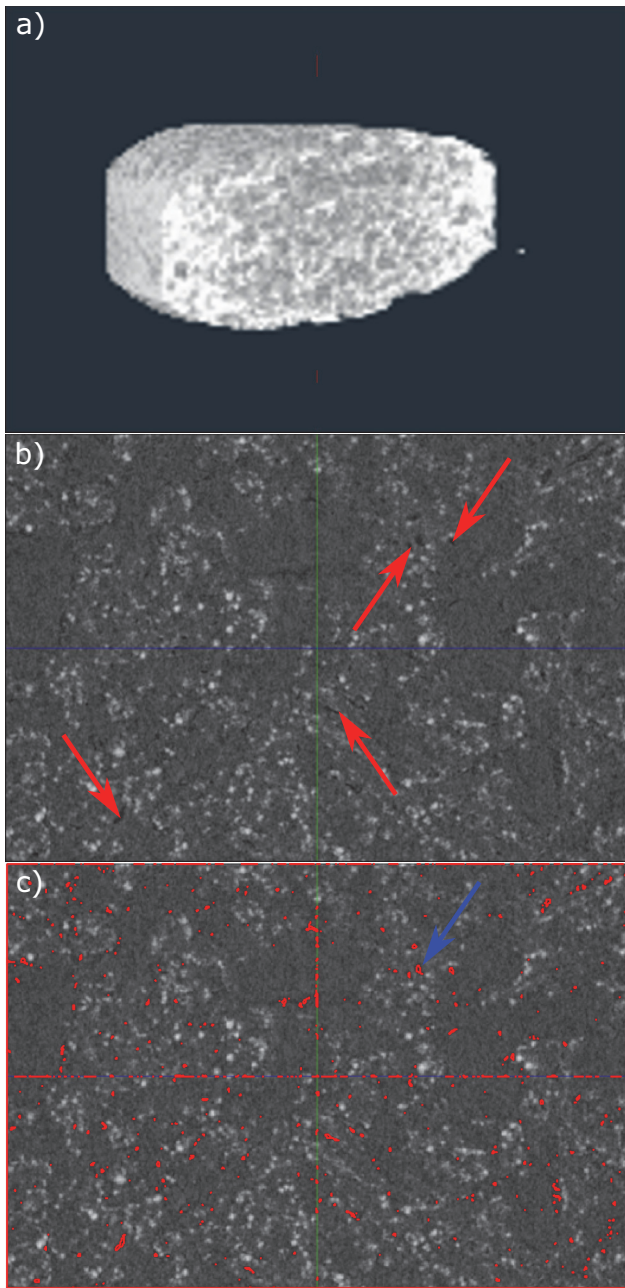
All brightness-mode video clips, recorded at 7.5 frames per second, were converted to still frames. A total number of 9450 frames was processed using MATLAB<sup>®</sup>. The frames were cropped to the 60 centre-most imaging lines relative to the tablet. For each imaging line in each brightness-mode image, 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.

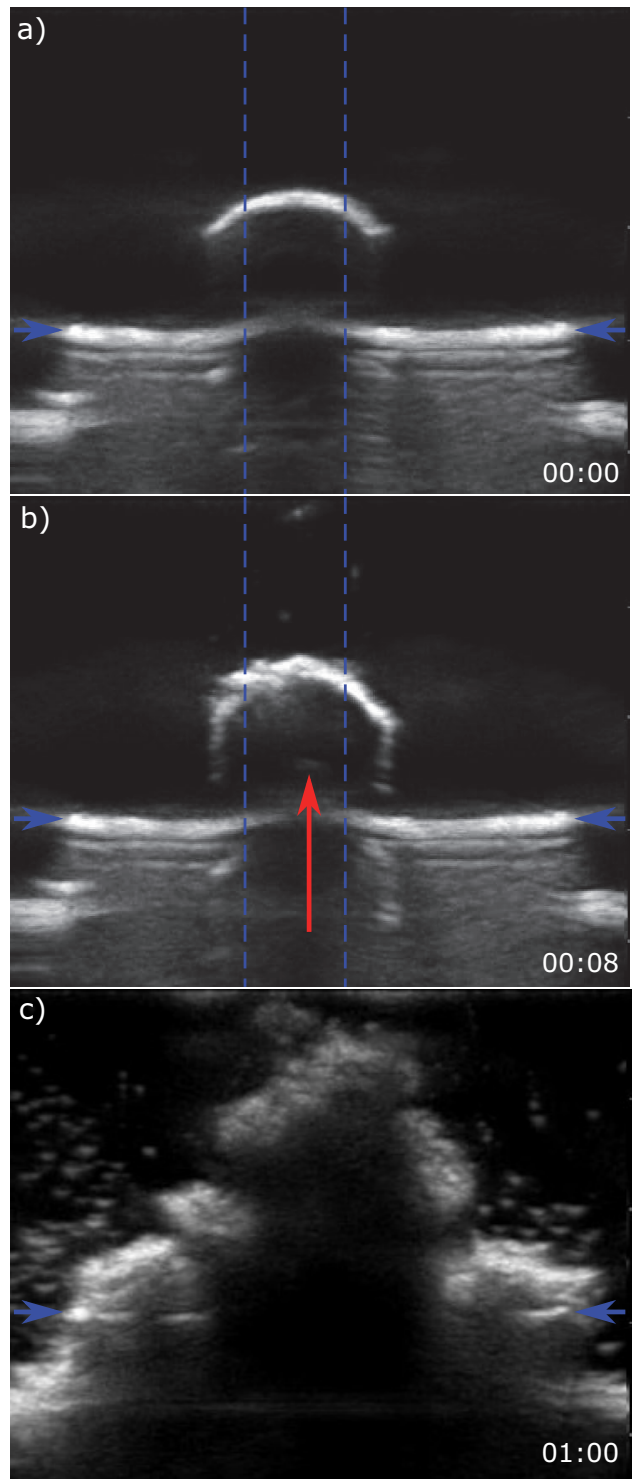
## 3 Results and discussion

Figure 2 demonstrates a tomographic  $\mu$ CT image with a three-dimensional representation of a tablet cross-section and close-ups thereof. Microscopic cavities up to  $9\ \mu\text{m}$  in diameter could be appreciated in the close-up images. Moreover, some microcavities 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  $\mu$ CT 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- $\mu$ m diameter has been marked by a blue arrow (c). Frames (b) and (c) correspond to  $1.6 \times 1.1$ -mm<sup>2</sup> 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  $\mu$ CT 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  $162 \pm 16 \mu\text{m s}^{-1}$ . 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

Research funding: This work has been supported by the National Research Foundation of South Africa, Grant Number 127102, and by the Academy of Finland, Grant Number 340026. Conflict of interest: Authors state no conflict of interest. Informed consent: Authors state that informed consent is not applicable. Ethical approval: Authors state that no ethical approval was required for this research as no human or animal samples or data were used.

## References

- [1] Leskinen JTT, Simonaho S-P, Hakulinen M, Ketolainen J. In-line ultrasound measurement system for detecting tablet integrity. *Int J Pharm* 2010;400:104–113.
- [2] Simonaho S-P, Takala TA, Kuosmanen M, Ketolainen J. Ultrasound transmission measurements for tensile strength evaluation of tablets. *Int J Pharm* 2011;409:104–110.
- [3] Leskinen JTT, Simonaho S-P, Hakulinen M, Ketolainen J. Real-time tablet formation monitoring with ultrasound measurements in eccentric single station tablet press. *Int J Pharm* 2013;442:27–34.
- [4] Zhou Y, Gu N, Yang F. *In situ* microbubble-assisted, ultrasound-controlled release of superparamagnetic iron oxide nanoparticles from gastro-retentive tablets. *Int J Pharm* 2020;586:119615.
- [5] Postema M, Smith AJ. Tablet processing unit. *Int Patent* WO2010/055337 2010.
- [6] Carlson CS, Anderton N, Pohl A, Smith AJ, Kudo N, Postema M. Ultrasonic tablet disintegration for controlled digestion. *Proc UltraSonic Electronics Symp* 2021;42:2E2–4.
- [7] Carlson CS, Anderton N, Pohl A, Smith AJ, Kudo N, Postema M. Rapid tablet swelling and disintegration during exposure to brightness-mode ultrasound. *Jpn J Appl Phys* 2022;61:ac467f.
- [8] Postema M, de Jong N, Schmitz G. The physics of nanoshelled microbubbles. *Biomed Tech* 2005;50(S1):748–749.
- [9] Mienkina MP, Postema M, Hansen C, Schmitz G. Modelling ultrasonic backscattering of an SPIO-MRI contrast agent. *Biomed Tech* 2005;50(S1):750–751.
- [10] Zou J, Hannula M, Misra S, Feng H, Labrador RH, Aula AS, et al. Micro CT visualization of silver nanoparticles in the middle and inner ear of rat and transportation pathway after transtympanic injection. *J Nanobiotechnology* 2015;13:5.
- [11] Tamminen I, Lehto K, Hannula M, Ojansivu M, Johansson L, Kellomäki M, et al. A tube-source X-ray microtomography approach for quantitative 3D microscopy of optically challenging cell-cultured samples. *Commun Biol* 2020;3:548.
- [12] Hyväluoma J, Kulju S, Hannula M, Wikberg H, Källi A, Rasa K. Quantitative characterization of pore structure of several biochars with 3D imaging. *Environ Sci Pollut Res* 2018;25:25648–25658.
- [13] Palmroth A, Pitkänen S, Hannula M, Paakinaho K, Hyttinen J, Miettinen S, et al. Evaluation of scaffold microstructure and comparison of cell seeding methods using micro-computed tomography-based tools. *J R Soc Interface* 2020;17: 20200102.
- [14] Virta J, Hannula M, Tamminen I, Lindfors K, Kaukinen K, Popp A, et al. X-ray microtomography is a novel method for accurate evaluation of small-bowel mucosal morphology and surface area. *Sci Rep* 2020;10:13164.