Ultrasonic tablet disintegration for controlled digestion

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1. Introduction

Controlled disintegration of tablets is relevant for chemical consistency checks of pharmaceutical tablets in vitro and for rapid gastric uptake of orally administered tablets in vivo. This feasibility study investigates if pulsed diagnostic brightness-mode ultrasound speeds up tablet disintegration.

Although ultrasonics have been used in the compaction of solid materials[1] and the visualisation of tablets in the stomach,[2] ultrasonic technology is not yet considered as a default methodology for the disintegration of tablets.[3] Nevertheless, long-pulsed ultrasound from single-elements has been observed to speed of the disintegration of tablets.[4] This speeding up of tablet disintegration has been associated with the friction from oscillating microscopic air pockets inside the tablet.[5]

The four stages identified in the disintegration process of sugar-coated tablets are: [4,5] first formation of cracks in the sugar-coated tablet surface; first visible expansion of the tablet; first gas and/or fragment release; onset of collapse of the tablet. In this paper, we subjected tablets to brightness-mode ultrasound whilst timing the disintegration stages. In addition, tablet fragments were subjected to high-speed photography.

2. Materials and Methods

Two experimental setups were used. The first setup was used to study gas release from tablet fragments with pulsed ultrasound from a single element. The second setup was used to study the full disintegration process of entire tablets with diagnostic brightness-mode ultrasound from a commercial clinical probe.

The single-element experiments were carried out in the 0.2-mL observation chamber of a high-speed photography system.[6] A tablet was manually crushed, after which 1-mm fragments were added to the observation chamber that was filled with 0.2 ml of distilled water. The observation chamber was placed under an Eclipse Ti inverted microscope (Nikon Corporation, Tokyo, Japan) with a Plan Apo 10× (N.A. 0.45) objective lens. An

HPV-X2 high-speed camera (Shimadzu, Nakagyo-ku, Kyoto, Japan), operating at 10 million frames per second, was coupled to the microscope.[6] The tablet fragments were subjected to ultrasound bursts during camera recording. The sonication equipment was described by Kudo et al.[6] A burst comprised a 20-cycle sine pulse, with a centre frequency of 1 MHz and an input voltage less than 5 V, to prevent any thermal effects.[7,8]

The brightness-mode experiments were carried out in the tank shown in **Fig. 1**. The setup comprised a HPL850 classic food container (LocknLock Co., Ltd., Seoul, South Korea) filled with 250 ml Randburg tap water. Either a C60x 5–2 MHz curvilinear or an HFL38x 13–6 MHz linear probe of a SonoSite® M-Turbo® sonography device (FUJIFILM SonoSite, Inc., WA, USA) was clamped with the probe face directed towards the bottom of the container. A tablet was placed in the container under the probe face at time $t=0$. Videos of the progression of tablet disintegration were captured using a Huawei P30
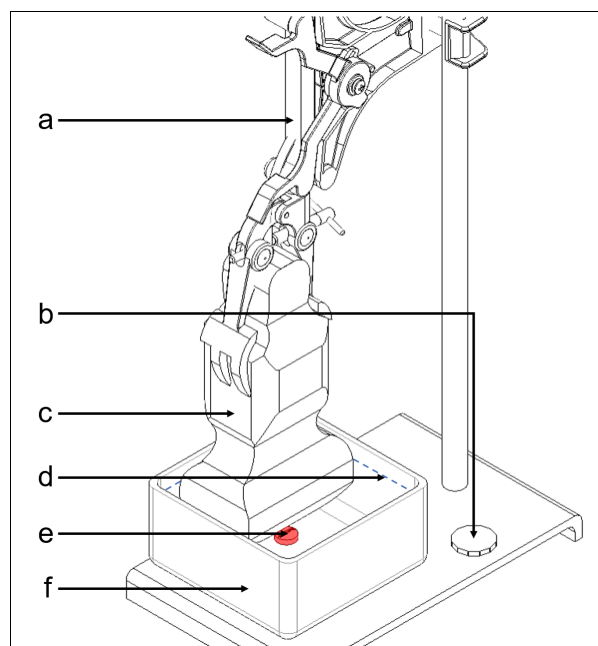

Fig. 1 Line drawing of the brightness-mode setup, consisting of a burette clamp and stand (a), a £1 coin for scale (b), an ultrasound probe (c), water, whose level is indicated by a blue dashed line (d), a pill highlighted in red (e), and a plastic Tank (f).

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lite cell phone camera. The ultrasound system was operating in pulsed brightness mode with a mechanical index of 0.8.

We considered a trinity of analgesia tablets: Ibuprofen (Special Concept Development BV, Rotterdam, Netherlands), Panado® (Adcock Ingram Ltd, Midrand, South Africa), and Loxoprofen (Kokando Pharmaceutical Co., Ltd, Amagasaki, Hyogo, Japan). The latter tablets were exclusively used in the high-speed photography experiments, for logistic reasons.

A total number of 10 high-speed video sequences, 11 regular-speed video clips, and 28 still-frame images were recorded. The videos and images were clipped, segmented, and analysed using the matrix laboratory MATLAB® (The MathWorks, Inc., Natick, MA, USA).

3. Results and Discussion

Fig. 2 shows eight frames of a representative example from the high-speed video recordings of tablet fragments. The frames highlight two air pockets on a tablet fragment surface. 18 individual nucleation events were observed during the 20 cycle burst. The resting diameters of the two air pockets were 8 μm and 3 μm, respectively. Assuming a speed of sound in the tablet greater than 1500 m/s, the resonance frequency of these pockets must be greater than 2 MHz.

Fig. 3 shows four frames of a representative example from the regular-speed video recordings of a disintegrating tablet. The time of the first visible sign of tablet fragments avalanching from the tablet (cf. Fig. 3d) was defined as the onset of collapse for the experiments with Ibuprofen and Panado®.

Table I shows the mean times until the onset of tablet collapse, was visibly observed, for Ibuprofen and Panado®. Ibuprofen was observed to disintegrate after multiple minutes, whilst Panado® was observed to disintegrate after approximately one minute. For both tablet types, the disintegration time with ultrasound was roughly three quarters of the disintegration time without ultrasound. We did not observe significant
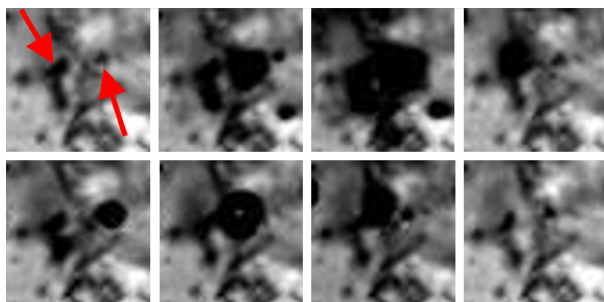
Fig. 2 Analgesia tablet fragments before, during and after sonication. Two nucleation sites are indicated by red arrows. Each frame corresponds to $50 \times 50 \ \mu m^2$.
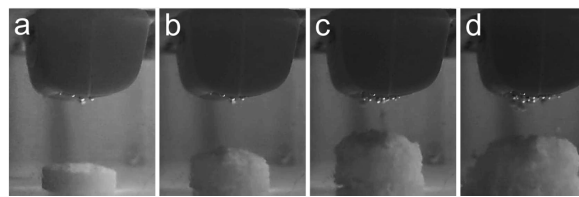
Fig. 3 Stages of tablet disintegration: original tablet (a), expansion of tablet (b), gas/fragment release (c), and onset of collapse (d).

differences between the experiments with single-element transducers and those with commercial multi-element probes.

Table I   Time to reach the onset of collapse.

	Ultrasound	No ultrasound
Ibuprofen	17 ± 7 min	23 ± 7 min
Panado®	50 ± 8 sec	65 ± 14 sec

4. Conclusions

We demonstrated the feasibility of brightness-mode-assisted tablet disintegration at diagnostic amplitudes. Furthermore, we showed ultrasound-induced nucleation on tablet fragment surfaces, confirming the previous hypothesis that gas pockets are involved in the disintegration process.

Ultrasound-assisted controlled disintegration of solid mm-sized items has applications in chemical consistency checks of pharmaceutical tablets in vitro, in rapid gastric uptake of orally administered tablets in vivo, and potentially even in fracturing of kidney stones.

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