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Rough handling accelerates tablet swelling in ultrasound

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1. Introduction

Oral pharmaceutical tablets are typically swallowed in whole, after which slow disintegration in the stomach facilitates steady drug release. Ultrasound has been used to monitor tablet integrity,[1)] to measure tablet swelling,[2)] and to accelerate tablet disintegration.[3)] High-speed footage revealed ultrasonic nucleation of microscopic gas pockets inside analgesia tablet fragments.[3)] The presence of these microscopic pockets has been speculated to be the cause of accelerated disintegration under sonication.[3)] Significant differences in swelling rates of various batches of otherwise identical analgesia tablets were attributed to minute differences in compaction during the manufacturing process.[2)] However, the effect of accidental or purposeful rough handling of tablet batches was not ruled out. One might wonder, whether rough handling might cause internal damage, which in turn might change the tablet dissolving times.

The purpose of this study was to quantify the influence of rough tablet handling on the swelling rate of tablets. It has been noted that prior studies had been carried out with drug-containing tablets. Although it has been presumed that the hydrophobic tablet matrix is responsive to ultrasound, this was not experimentally shown. In this study, tablets comprising matrix without therapeutic component have been used.

2. Materials and Methods

Tablets were manufactured from Avicel PH102 micro-crystalline cellulose powder (FMC Agro Ireland Limited, Cork, Ireland), a commonly used tablet matrix.[4)] The powder was compacted under 1.5-MPa compression to form cylindrical tablets of 0.4-g mass, 10-mm diameter, and 4.4-mm height. Before the rough handling and swelling experiments, the tablets were tested for their responsiveness to ultrasound, by collecting footage of 5-mg tablet fragments subjected to a 3-cycle focused ultrasound pulse with a 1.0-MHz centre frequency and a 1.1-MPa peak-negative pressure, recorded at ten million frames per second with a high-speed camera system.[5)] The rough tablet handing was done with an experimental setup allowing for the release of a PROF DIN934 M10 I8I electro-galvanised hexagonal nut (Keski Corporation, Helsinki, Finland) at 82-cm height onto a tablet sandwiched between two 1-SHP coins. The impact of the nut on the tablet was recorded using a FASTCAM MC1 high-speed camera (Photron (Europe) Limited, West Wycombe, Bucks, United Kingdom) with a 8–50mm zoom lens (Waveshare Electronics, Shenzhen, China). A schematic drawing of this experimental setup is shown in **Fig. 1**. Ten tablets were subjected to a nut drop.

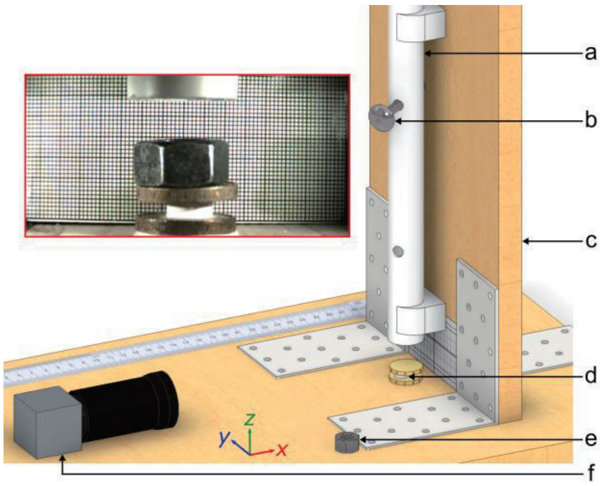

Fig. 1 Schematic drawing of the experimental setup for rough tablet handling, comprising a pipe of 22-mm bore diameter (a) with a nut release mechanism at 82-cm height (b), fixated on a wooden frame (c), with the pipe exiting above a tablet sandwiched between two 1-SHP coins (d) impacted by the nut (e), and a high-speed camera at a 30-cm horizontal distance (f). The inlay frame was captured during nut impact. The line density of the mesh corresponds to 1/mm.

The swelling rate of tablets was determined using the same setup as previously described.[3)] In short, an HFL38x 13–6MHz linear probe of a SonoSite® M-Turbo® sonography device (FUJI-

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FILM SonoSite, Inc., WA, USA) was clamped with the probe face directed towards coin reflector placed on the bottom of a water container. The device converted two-way travel times to perceived distances using a fixed value of 1540 m s^{-1} for the speed of sound. For each swelling experiment, a tablet was placed on the coin reflector. The swelling rate was determined by fitting a linear function through the perceived distance through the central axis of the probe to the first reflector as a function of time. This procedure was performed on ten unhampered and ten roughly handled tablets.

3. Results and Discussion

Fig. 2 shows high-speed footage of a 5-mg tablet fragment subjected to a 3-cycle focused ultrasound pulse. The recording demonstrates pulsation of micropockets inside the tablet fragment, similar to the footage presented previously.[3] Hence, the tablet matrix used was responsive to ultrasound.

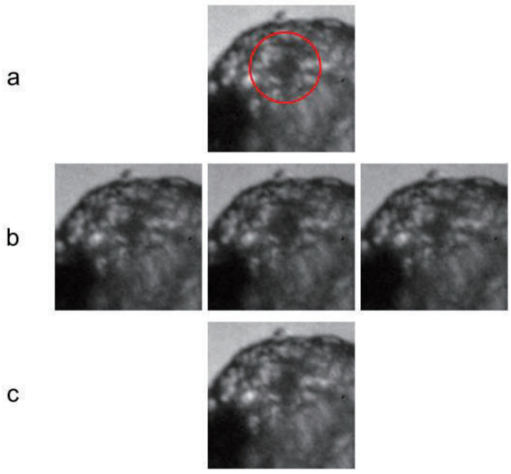

Fig. 2 High-speed footage of a tablet fragment before (a), during (b), and after sonication (c). A pulsating micropocket has been indicated by a red circle. Each frame corresponds to a 40×40-μm^2 area.

Fig. 3 shows perceived distances between probe face and tablet surface as a function of time for selected experiments. The line fitted through the measured data yielded a swelling rate of 179±9 μm s^{-1} for unhampered and 230±38 μm s^{-1} for roughly treated tablets. The greater swelling speed of roughly treated tablets may be attributed to increased interconnectivity of pre-existing micropockets inside tablets due to the internal damage caused by rough handling. This outcome implies that rough handling of tablet batches, for example during packaging or during transport, may not just be of influence on the swelling and therefore on the disintegration after a tablet has been swallowed, but also on the drug release rate. The latter possibility is an unwanted effect that should be taken into account by manufacturers, especially of modified-release tablets. Moreover, it would be safe to assume that the five-second rule does not apply to drugs in tablet form.

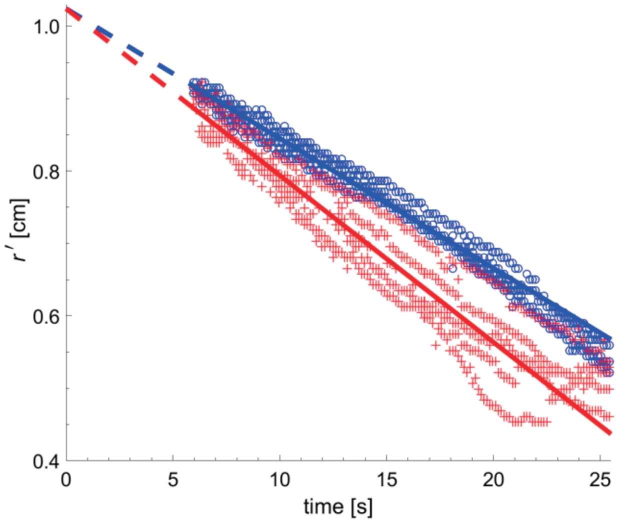

Fig. 3 Perceived distance as a function of time for unhampered (blue) and roughly handled tablets (red). The linear swelling rates have been computed and plotted.

4. Conclusions

Our experiments showed pulsation of micropockets inside a tablet fragment, confirming the prior hypothesis that the tablet matrix was responsive to ultrasound. Swelling rates of tablets that had undergone rough handling were higher than those of identical unhampered tablets. This finding is thought to have direct implications on drug release rates. Consequently, great care should be taken when handling, packaging, and transporting pharmaceutical tablets.

Acknowledgements
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References
1) J. T. T. Leskinen et al., Int. J. Pharm. **400**, 104 (2010).
2) C. S. Carlson et al., Jpn. J. Appl. Phys. **61**, SG1030 (2022).
3) C. S. Carlson et al., Proc. 42nd Symp. UltraSonic Electronics, 2021, 2E2-4.
4) G. Thoorens et al., Int. J. Pharm. **473**, 64 (2014).
5) N. Kudo, IEEE Trans. Ultrason. Ferroelect. Freq. Control **64**, 273 (2017).