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Mazzoni, Chiara; Slipets, Roman; Ilchenko, Oleksii; Thamdrup, Lasse Højlund Eklund; Nielsen, Line Hagner; Boisen, Anja

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## Stability of amorphous indomethacin loaded into microcontainers with different shapes and sizes

Chiara Mazzoni, Roman Slipets, Oleksii Ilchenko, Lasse Højlund Eklund Thamdrup, Line Hagner Nielsen, Anja Boisen

*The Danish National Research Foundation and Villum Foundation's Center for Intelligent Drug Delivery and Sensing Using Microcontainers and Nanomechanics (IDUN), Department of Health Technology, Technical University of Denmark, Ørstedes Plads 345C, 2800 Kgs. Lyngby, Denmark*

Learning objectives:

1. Explain the idea behind the use of microcontainers to stabilize amorphous poorly soluble drugs
2. Evaluate if the shape and size of microcontainers can affect the stability of the confined drug
3. Discuss if the crystallization of the confined drug depends on the material of the microcontainers

**Introduction:** Microcontainers are polymeric cylindrical microdevices with only one side open<sup>1,2</sup>, and they can be fabricated in different sizes and shapes. A technique to enhance solubility and dissolution rate of poorly water soluble drugs is to change their solid state form from crystalline to amorphous. Previously, it has been shown that the stability of amorphous indomethacin confined in SU-8 cylindrical microcontainers was enhanced compared to bulk indomethacin<sup>3</sup>.

The aim of this study was to investigate if the stability of amorphous indomethacin was depending on the shape, size or fabrication material of the microcontainers.

**Methods:** Microcontainers were fabricated in silicon using UV-photolithography and anisotropic dry etching resulting in circular, triangular and squared devices. Every shape was fabricated in three different sizes on a chip, each containing 100 microcontainers. The dimensions of the microcontainers can be found in Table 1. All the microcontainers were filled manually with crystalline indomethacin ( $\gamma$ -form) (Figure 1). Each chip was placed on a heating plate at 200°C for 10 s to melt indomethacin followed by quench-cooling in liquid nitrogen. As control sample, bulk (non-confined) indomethacin was melted and cooled as described above. All the samples were stored at 30°C and at  $29 \pm 0.3$  % relative humidity for up to 30 days. For evaluation of the solid state form of indomethacin, Raman spectroscopy was used. Every third day, one spectrum for all the microcontainers (100 per shape and size) and the control sample were measured to evaluate if the indomethacin was in its crystalline or amorphous form.

**Results:** The powder sample resulted to be crystalline already after three days, whereas microcontainers stabilized amorphous indomethacin for more than 27 days. After day 15, the number of triangular microcontainers with amorphous indomethacin was higher than for squared and circular microcontainers. More than 50 % of circular and squared microcontainers had still amorphous drug in them after 27 days. In addition, indomethacin was found to be amorphous in more than 50 % of the triangular microcontainers after 30 days. During the study, squared and circular microcontainers showed a similar behavior, stabilizing indomethacin for 27 days. These data confirmed the results obtained by Nielsen et al.<sup>3</sup> showing that the microcontainers material does not affect the stability of indomethacin.

**Conclusions:** Amorphous indomethacin confined in microcontainers is stable for 26 days more than when in bulk form and the triangular shape show the highest effect as a confinement stabilizer.

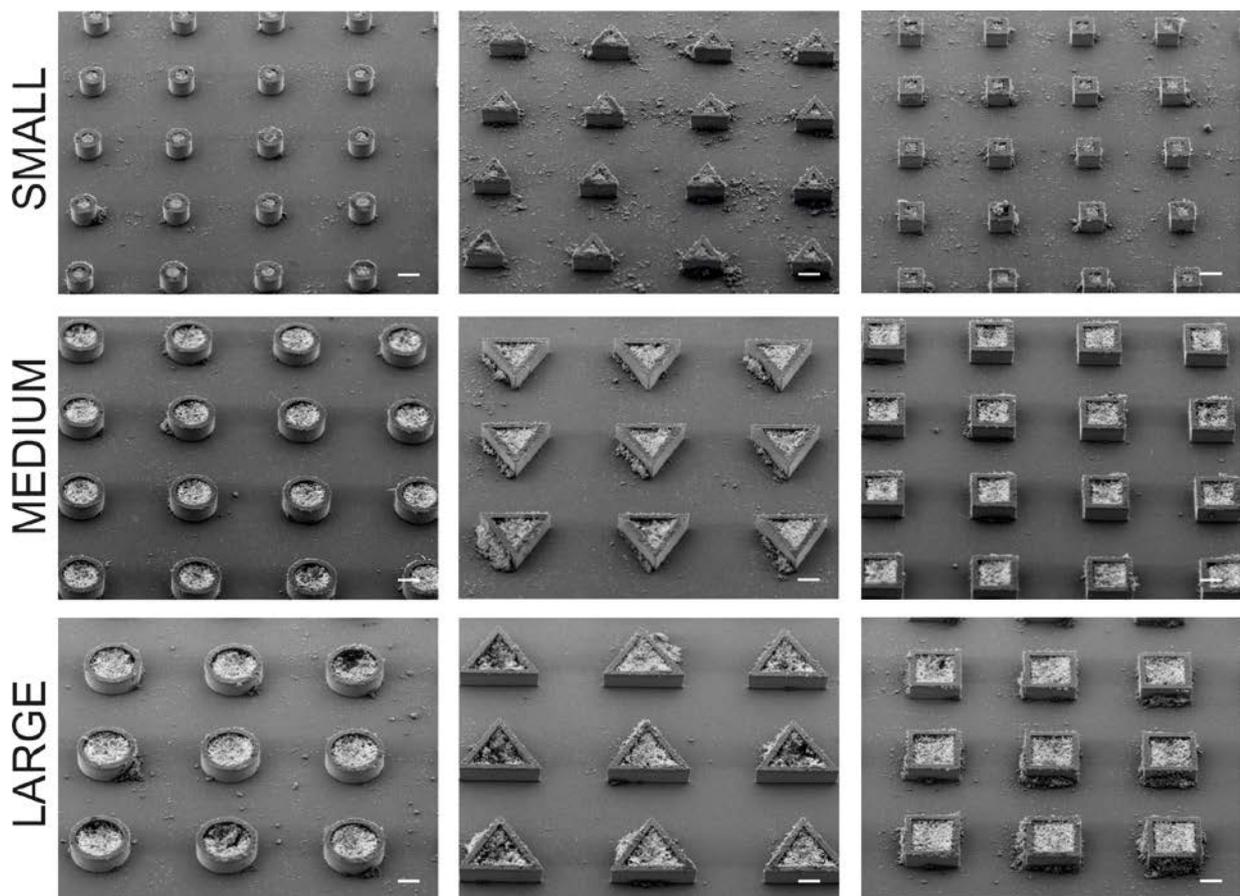
[1–3][4]

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**Fig. 1:** SEM images of microcontainers filled with crystalline indomethacin with circular (left column), triangular (middle column) and squared shapes (right column) in small, medium and large sizes. The scale bars represent 100  $\mu\text{m}$ .

**Table 1:** Dimensions of the various microcontainers used in this study.

SIZE	Circular microcontainers internal diameter	Triangles microcontainers internal side length	Squares microcontainers internal side length
Small	68 $\mu\text{m}$	91 $\mu\text{m}$	60 $\mu\text{m}$
Medium	169 $\mu\text{m}$	226 $\mu\text{m}$	149 $\mu\text{m}$
Large	219 $\mu\text{m}$	293 $\mu\text{m}$	195 $\mu\text{m}$