LASER ABLATION OF MELOXICAM IN LIQUID ENVIRONMENT

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1. INTRODUCTION

In the development of new pharmaceutical formulation strategies, the need for innovative drug particle size reduction approaches has significantly increased during the past decades. In the US poorly soluble compounds represent 40% of the top 200 marketed oral drugs and 33% of the drugs listed in the US Pharmacopeia. Additionally, 75% of compounds under development and 90% of new chemical entities are poorly soluble [Rodriguez 2015]. A frequently used method to improve the dissolution rate and transport characteristics of these drugs is particle size reduction. Thereby faster absorption and more effective cellular uptake can be achieved [Mosharraf 1995, Rasenack 2003].

Since pulsed laser ablation is a well-established technique for particle generation from both inorganic and organic materials, pharmaceutically relevant investigations became interested in using laser ablation as a particle size reduction technique [Sylvestre 2011, Ding 2014, Hopp 2018, Singh 2020, Gera 2020]. In this systematic study we demonstrate the application of pulsed laser ablation for the fragmentation of drug particles in liquid environment.

2. EXPERIMENTAL

Pulsed laser ablation in liquid (PLAL) was used to generate particles from meloxicam (mx.), a medically relevant poorly water-soluble nonsteroidal anti-inflammatory drug (NSAID). As targets, pastilles were pressed from commercially available meloxicam powder (EGIS Ltd, Budapest, Hungary) by a hydraulic compactor at 175 MPa pressure. To determine the suitable parameter range for ablation, nanosecond (ns) laser pulses of different wavelengths (248 nm, 532 nm and 1064 nm) and fluences (~ 3-13 J/cm^2) were investigated in distilled water environment [Nagy 2019].

To characterize the generated particles several methods were applied. Fourier transform infrared spectroscopy (FTIR) was used for chemical analysis. The size-distribution and morphology of the generated particles were studied by scanning electron microscopy (SEM). The crystallinity was investigated by X-ray powder diffraction (XRPD). Heat induced phase transitions of the PLAL generated particles were detected by differential scanning calorimetry (DSC) [Hopp 2018].

The ablation dynamics were studied using the time-resolved pump-probe shadowgraphy technique. Fast photography took place with a nanosecond time resolution. The ablation process was investigated at three different fluences using 532 nm laser wavelength.

3. RESULTS AND DISCUSSION

3.1. Characterization of the generated particles

The FTIR spectra of PLAL produced particles match the spectra of the original meloxicam powder in the investigated fluence range at all applied wavelengths (***Figure 1.***). The presence of the characteristic peaks indicates that chemically identical meloxicam particles can be generated from a drug pastille by PLAL [Hopp 2018, Nagy 2019].

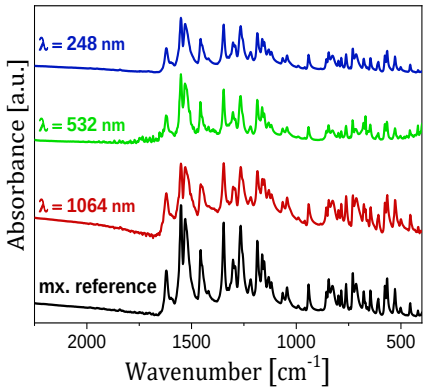


Figure 1. FTIR spectra of PLAL generated meloxicam particles (F= 9.4 J/cm^2) and reference meloxicam (mx.) powder.

SEM images revealed significant reduction in the size of the meloxicam particles as compared to the commercially available reference meloxicam powder. The morphology of the PLAL generated particles resembled broken pieces, scattered crystals, indicating that mechanical effects could have been the most relevant factors during fragmentation (**Figure 2.**) [Hopp 2018, Nagy 2019].

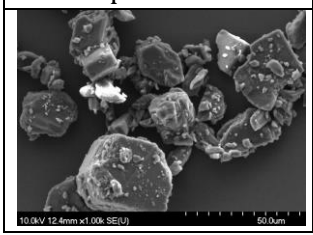
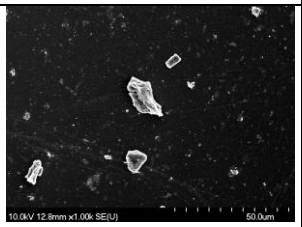
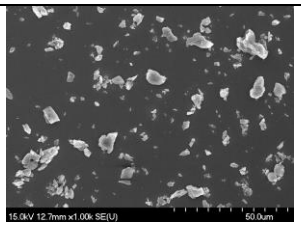
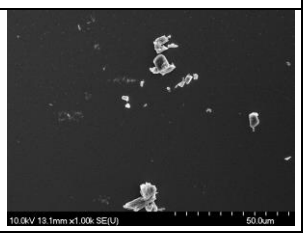
Reference meloxicam powder	248 nm	532 nm	1064 nm
			

Figure 2. SEM images of the original meloxicam powder particles and of the particles obtained from the meloxicam suspensions produced at different wavelengths (Mag.: 1000x, scale 50.0 μm)

The 532 nm laser wavelength provided the highest ablation yield. Size-distributions were determined using ImageJ® image processing and analysis software [Hopp 2018, Nagy 2019].

In case of the PLAL generated particles XRDP characterization showed slight decrease (~ 7%) in the crystallinity and DSC investigations showed an approximately 20 °C shift to the lower temperatures in the melting point compared to the commercially available meloxicam powder. Both of these measurements indicate that PLAL causes the amorphization of meloxicam to some degree [Hopp 2018].

3.2. Characterization of the ablation process

Based on the time-resolved fast photography observations, three main parts of the ablation process can be distinguished (***Figure 3.***). In the first few hundred nanoseconds the refractive index of the medium changes and numerous small bubbles appear. Evaluating the recorded sequence of pictures, the formation and propagation of the wavefront was constructed. The velocity of the wave propagation was found to be 1480 m/s, which is the velocity of sound in water. This means, that the shockwaves slow down very quickly (after a few 10 ns) and become acoustic waves. The second part, between a few and a few hundred microseconds, is the time period when the formation and pulsation of the cavitation bubble takes place. The third part, a few milliseconds after the laser pulse, is when the cavitation bubble collapses and the ablated particles are released from its interior into the distilled water.

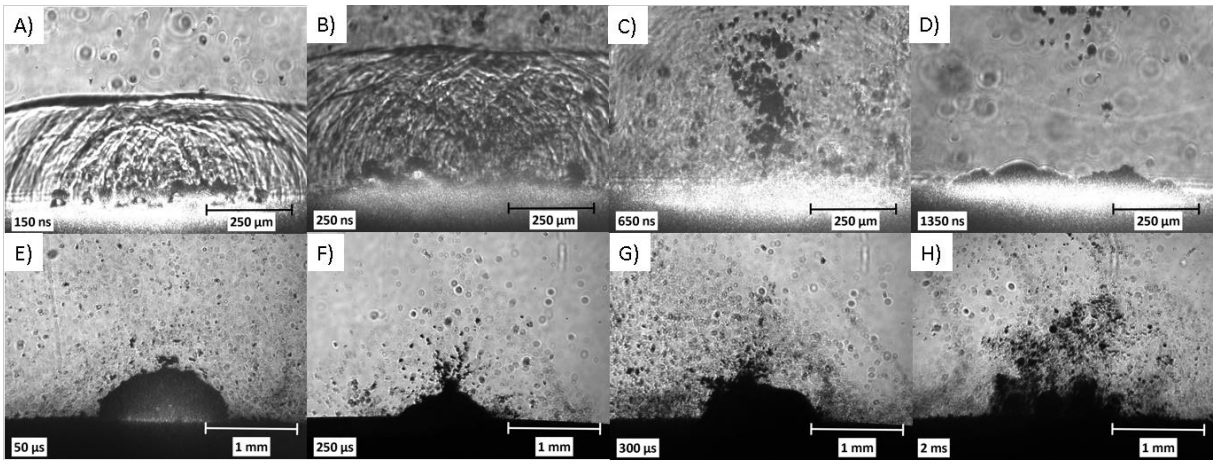


Figure 3. Time-resolved fast photography pictures. The sequence of the pulsed laser ablation (λ=532 nm, F = 6 J/cm^2) of a meloxicam pastille. Ablation process as discussed in the text: part one: A)-C), part two: D)-G) and part three: H).

4. CONCLUSIONS

PLAL proved to be a non-damaging, clean (chemical free) and effective way of generating few micrometre and sub-micrometre sized meloxicam particles. The size of PLAL produced particles was around one-tenth of the average size of the commercially available meloxicam powder particles and comparable with the size of particles produced by conventional techniques (grinding, wet milling). Time-resolved fast photography provided insight into the process of the ablation of the drug pastille.

5. ACKNOWLEDGEMENTS

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