STUDY OF THE FRAGMENTATION OF SOLID DRUG PARTICLES DURING ABLATION WITH DIFFERENT PULSE LENGTH LASERS

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1. INTRODUCTION

A large number of pharmaceutical drugs are poorly water-soluble and have relatively low bioavailability, therefore significant efforts have been made to develop methods for improving their solubility and dissolution rate. Due to its high efficiency, the drug particle size reduction is one of the frequently used methods, since the increase of specific surface (surface to volume ratio) leads to enhanced dissolution rate and a higher bioavailability during the administration [Mosharraf 1995, Shegokar 2010]. Besides the different conventional approaches applied for size reduction, such as grinding, wet milling, forming of solid dispersions for which the smallest attainable sizes remain in the micrometer regime, in the last decade several studies aimed the fragmentation of drug particles by means of pulsed laser ablation. While laser ablation in gas or liquid environments has been widely used for nanoparticle production from inorganic target materials, there are much fewer studies on the production of sub-micrometer sized particles of organic or pharmaceutical compounds with this method [Sylvestre 2011, Ding 2014, Hopp 2018, Gera 2020, Ambrus 2020].

In this study we compare the main properties of the particles produced by pulsed laser ablation of three poorly water-soluble nonsteroidal anti-inflammatory drugs (NSAID) (ibuprofen, meloxicam and niflumic acid) tablets when using of various laser types with pulse lengths in nanosecond, picosecond and femtosecond range.

2. EXPERIMENTAL

The target tablets were produced using a hydraulic compactor at 175 MPa pressure from the following commercially available drug powders:

- Ibuprofen (α-Methyl-4-(isobutyl) phenylacetic acid): white color, particle size of 15.3 μm (d(0.5)), 75-77 °C melting point, 157 °C boiling point, 230 to 250 °C decomposition temperature;
- Meloxicam (4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-benzothiazine-3-car-boxamide-1,1-dioxide): yellow color, particle size of 3.78 μm (d(0.5)), 100% crystalline, 254 °C melting/decomposition temperature;
- Niflumic acid (NIF) (2-(3-(trifluoromethyl)-phenyl)-amino)-3-pyridinecarboxylic acid, white color, 18.85 μm (d(0.5)) particle size, 203 °C melting/decomposition temperature.

Irradiation of the targets was performed in ambient pressure using the following lasers:

- nanosecond range, with 1.5–12 J/cm^2 fluence:
  - KrF excimer laser: FWHM= 18 ns, λ= 248 nm, 10 Hz repetition rate
  - Nd:YAG laser: FWHM= 6 ns, λ= 532/1064 nm, 10 Hz repetition rate
- picosecond range, 0.45–4.35 J/cm^2 fluence
  - Nd:YAG laser: FWHM= 20 ps, λ= 355/532/1064 nm, 80 kHz repetition rate
- femtosecond range, 0.7–1.5 J/cm^2 fluence
  - Ti:sapphire: FWHM=135 fs, λ=800 nm, 10 Hz repetition rate

The ablated aerosol particles were transported by continuous air/N2 flow and collected on a filter membrane. The collected particles were analyzed by FTIR spectrometry and scanning electron microscopy (SEM). In some cases the size distribution of the produced aerosol particles was analyzed by Scanning Mobility Particle Sizer (SMPS) and Optical Particle Counter (OPC). For the nanosecond ablation the material removal process was studied with fast photographic method.

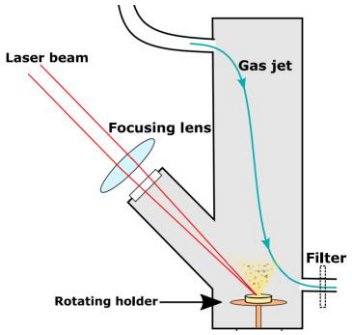

Figure 1. Experimental setup.

3. RESULTS AND DISCUSSION

3.1. Nanosecond ablation

FTIR spectra of the collected particles showed significant chemical decomposition in case of ablation at UV (248 nm) wavelength for all the three compounds, while the spectra maintained their characteristics for visible (532 nm) and NIR (1064 nm) wavelengths for all the fluencies, where notifiable material removal occurred [Gera 2020].

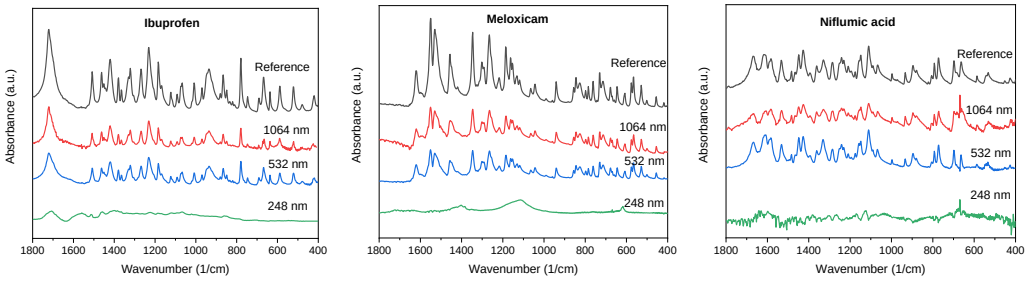

Figure 2. FTIR spectra of the nanosecond ablated drug particles.

SMPS measurements performed with 532 and 1064 nm showed that for a given compound the variation in fluence and wavelength had no strong effect on the size distribution of the particles transported by the gas stream. The smallest particles were detected in case of ibuprofen with modus values well below 100 nm, while the highest modus values with the broadest size distributions were obtained for the meloxicam particles. Practically there were no aerosol particles with sizes above 1 µm in the gas stream as demonstrated by OPC measurements. The number of ablated particles was the highest for meloxicam and the lowest for ibuprofen [Gera 2020].

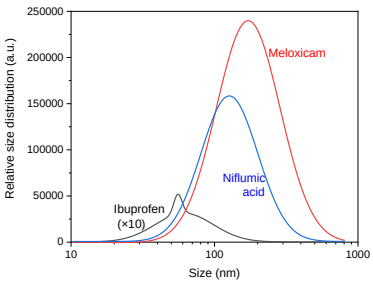

Figure 3. Characteristic SMPS size distributions of the particles ablated at 532 nm.

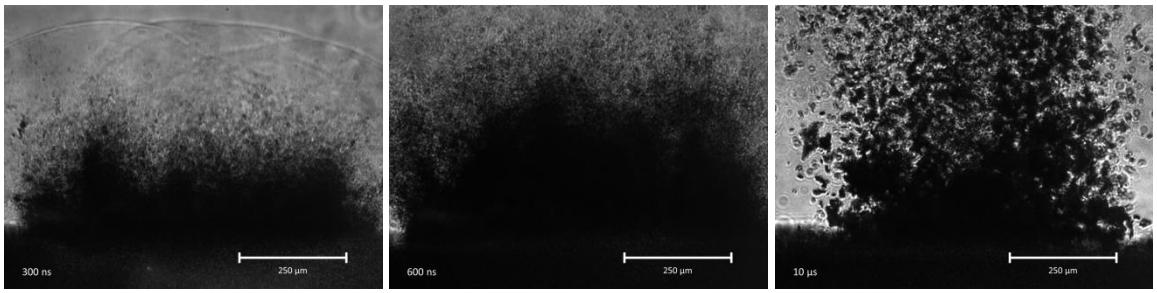

Figure 4. Material ejection when ablating meloxicam at 1064 nm and 9 J/cm^2 fluence.

Fast imaging revealed that the ablation mechanism is the same for all three drugs. The irradiation-generated shock wave is followed by a slightly slower material ejection. This material cloud is initially formed by large number of high speed fine particles (probably of sub-micrometer size) followed by the ejection of larger fragments in the micrometer range that have a lower speed. Particles much larger than those detected by SMPS are also ejected, however, these will probably sediment in the ablation chamber before reaching the gas extraction pipe and thus, the extracted gas stream will contain only smaller aerosol particles.

3.2. Picosecond ablation

In case of meloxicam and NIF the FTIR spectra of particles produced by ablation at 532 and 1064 nm showed good correspondence with that of starting materials, while in case of 355 nm wavelength the spectra were distorted in all the applied fluence range. Contrary to these, in case of ibuprofen measurable amount of ablated material was only obtained at 355 nm and the spectra maintained their characteristics as compared to the reference. The surface of the ibuprofen tablets was melted by the irradiation at all wavelengths, probably caused by the relatively low melting point as compared to the other two drugs.

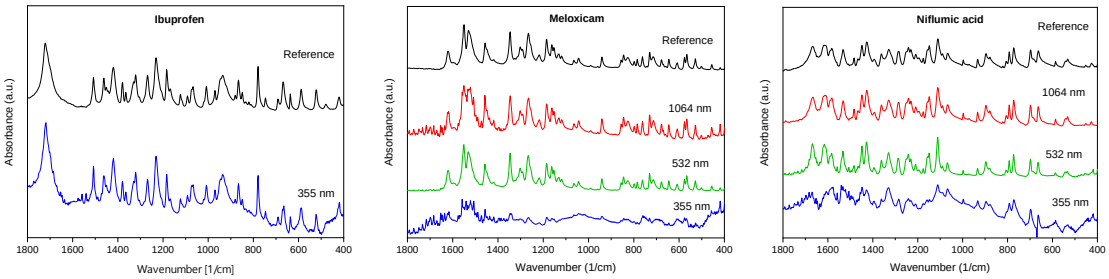

Figure 5. FTIR spectra of drugs ablated with picosecond laser pulses.

In this series of experiments the gas outlet point was places as close to the ablated surface as to extract all the ablated material and to deposit onto a membrane filter. As the SEM images of the deposits demonstrated, in cases of meloxicam and NIF the size of the produced particles ranged from ~100 nm up to 1-2 micrometers, much smaller than

the particle sizes of the original powders. In case of ibuprofen separated particles could not really be distinguished indicating their impact in molten state.

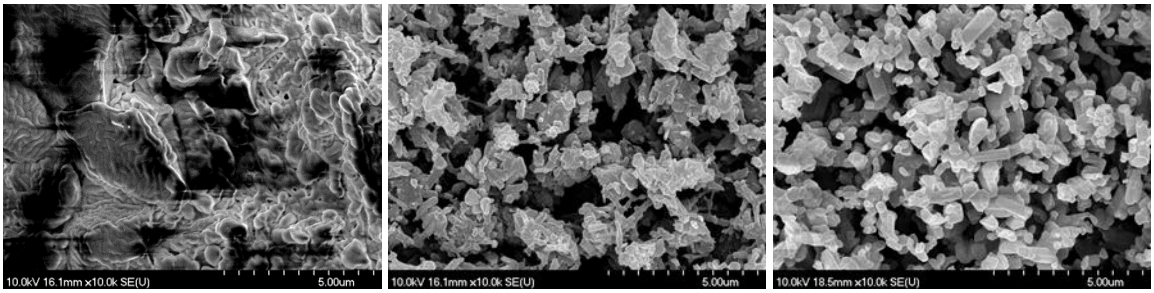

Figure 6. SEM image of ablatum collected after ibuprofen (left, 355 nm), meloxicam (middle, 532 nm) and niflumic acid (right, 532nm) ablation.

3.3. Femtosecond ablation

FTIR measurements of the particles produced by 800 nm femtosecond ablation of meloxicam showed good correspondence with the reference spectra in all the studied fluence range. The morphology of the particles strongly differed from those obtained at longer pulse durations. As shown on SEM images all the particles deposited on the filter membrane show spherical symmetry. Spherical particles in submicrometer size range have smooth surface, while the larger ones (up few micrometers) have surfaces covered with cracks and delaminated layers. The majority of the deposit is formed by spherical nanoparticles below 100 nm aggregated into longer chains.
The particle production by the femtosecond ablation showed much lower efficiency as compared to the nanosecond and picosecond ablation. First trials on NIF and ibuprofen showed similarly low ablation rate, therefore their ablation was not studied in detail.

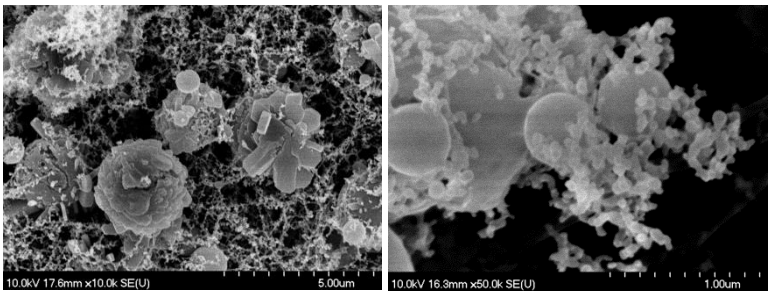

Figure 7. SEM images at different magnifications on ablatum collected from meloxicam.

4. CONCLUSIONS

Laser ablation of pressed drug tablets can be a promising way for fragmentation of poorly water-soluble drug materials and/or producing aerosols. While in the

commercially available powders of the studied compounds most of the mass exists in form of particles in tens of micrometer sizes, the particles generated by laser ablation ranges from about 100 nm to few micrometers. When using nanosecond and picosecond lasers the particles are mostly produced as solid fragments. The efficiency of size reduction is better in case of picosecond laser, as the nanosecond ablation removes from the targets larger material clusters, too, which sediment in bottom of the chamber. As compared to these, the femtosecond laser ablation produces spherical particles and nanoaggregates, while the ablation rate is relatively low.

5. ACKNOWLEDGEMENTS

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