Date: 28th of February 2019

DropTES 2018

Final Experiment Report

Interaction of laser exposed medicine droplets with target surfaces under microgravity conditions

Abstract

The interaction of UV laser radiation with pendant medicine droplets and their wetting properties on target surfaces has been investigated under the aegis of the United Nations Office for Outer Space Affairs (UNOOSA) within the Drop Tower Experiment Series (DropTES) Fellowship Programme. Experiments were conducted in microgravity conditions at Bremen Drop Tower, sponsored by the German Aerospace Center (DLR) Space Administration and the Center of Applied Space Technology and Microgravity (ZARM).

The DropTES 2018 experiment aimed to bring a new insight on the behaviour of medicine droplets in reduced gravitational environment. A novel aspect of the project represented droplets real time exposure and modification by UV laser beam, leading to new photoproducts with antimicrobial properties. The obtained droplets have been afterwards brought in contact with an aluminium target surface in order to study the evolution of wetting phenomena.

Since microorganisms can evolve into more virulent forms under microgravity conditions, astronauts and spacecraft surfaces may require treatment and decontamination, respectively, against onboard pathogens.

Team description

The DropTES 2018 team involved three PhD fellows and a MSc student from two renowned Romanian universities, such as University of Bucharest (UB) and University Politehnica of Bucharest (UPB), having Prof. Mihail-Lucian Pascu, the head of the Laser Spectroscopy Optics Group (LSO), as the team leader. The Romanian students are carrying out research activities at the Laser Department and the Center for Advanced Laser Technologies (CETAL) within the National Institute for Laser, Plasma and Radiation Physics (INFLPR).

Prof. Dr. Mihail-Lucian Pascu is the head of the LSO group of INFLPR as well as the PhD and MSc supervisor of Ágota Simon and Simona Stroescu. He graduated from the Faculty of Physics, UB in 1968. Prof. Pascu performed a PhD stage at the University of Texas in Dallas, USA and obtained his PhD in Optics, Lasers and Plasma Physics from UB in 1975. He was a Senior Research Scientist at the Institute for Physics and Technology of Radiation Devices since 1977 and Director between 1983 and 1990. He was at the same time member of the Scientific Council of the Faculty of Physics, UB and of the Executive Committee of the Central Institute for Physics. Prof. Pascu worked as a Science Officer at the European Commission DG RTD serving at COST Secretariat in the field Medicine and Health between 2001-2004. Prof. Pascu was Science Officer of the European Science Foundation at the COST Office between 2004 and 2006, where he was responsible for Biomedicine and Molecular Biosciences.
His experience in the field of laser techniques used to fight MDR by modifying existing medicines through exposure to laser radiation may prove helpful, due to the vast experience accumulated in this field, demonstrated by the scientific papers published in the last decade.
Prof. Pascu supervised and guided the DropTES 2018 team throughout the entire project, including preparatory and writing phases and evaluation of results.

Ágota Simon obtained a BSc degree in Biophysics at UB in 2012. Her BSc research project, entitled *Microfluidic flow-stretching of individual DNA molecules*, was performed within the Erasmus Programme in Prof. Dr. A.M. van Oijen's Single Molecule Biophysics Group, at the University of Groningen, under the supervision of Dr. Karl Duderstadt. Ágota received her MSc degree in Medical Biophysics at the Faculty of Physics, UB in 2014, with the thesis entitled *Interaction of phenothiazine solutions exposed to laser radiation with textile surfaces, in view of biomedical applications*, which involved studies at the LSO and participation in a Short Term Scientific Mission (STSM) within the COST MP1106 Network at the Engineering Fibrous Smart Materials Group (EFSM), at the University of Twente, led by Prof. Dr. Victoria Dutschk. Ágota participated in another STSM at Consiglio Nazionale delle Ricerche - Instituto per l'Energetica e le Interfasi (CNR-IENI), Genova, under the supervision of Dr. Michele Ferrari. She took part in the Spin Your Thesis! 2015 campaign as the team leader and at present she is involved in the Zero-Gravity Instrument Project (ZGIP) as the project leader. Currently, she is pursuing her Doctoral studies in the field of Optics, Spectroscopy, Plasma and Lasers, under the supervision of Prof. Pascu.
Within the DropTES 2018 project, Ágota was responsible for the technical redaction of the Experiment Proposal, Experiment Progress Reports (EPR) as well as the Final Experiment Report (FER). Besides the respective assignments, she handled and oversaw the design and assembly of the experimental set-up. Furthermore, she was in charge with studies regarding wetting phenomena in terrestrial and microgravity conditions. Also, Ágota managed the public outreach throughout the entire development of the project.

Bogdan-Ștefăniță Călin obtained a Bsc Engineering degree in Physical Engineering and a MSc degree in High Power Lasers and Particle Accelerators, both within UPB. He was a visiting researcher at Georgi Nadjakov Institute of Solid State Physics - Bulgarian Academy of Sciences (ISSP-BAS), Bulgaria, as part of the Research and Innovation Capacity Strengthening of ISSP-BAS in Multifunctional Nanostructures Project (INERA). Bogdan benefited of a Student Fellowship as part of the Joint Invention, Visibility and Excellence Project (JIVE). He is currently carrying out his Doctoral studies in *Multiphoton processing technologies applied in ultrafast laser microfabrication* within the Doctoral School of Applied Sciences of UPB under the supervision of Prof. Univ. Dr. Niculae Tiberiu Pușcaș.
The DropTES 2018 experiment linked to Bogdan's syllabus by designing and building experimental set-ups involving light sources and opto-mechanical components, applications of microstructures (2D/3D) obtained through ultrafast laser direct writing as well as integration of various passive components on lab-on-a-chip devices (biomimetics, integrated optics, microfluidics). Within the project, Bogdan designed the laser irradiation set-up as well as carried out the optical alignment and irradiation procedure of drug solutions. He also designed 2D/3D technical schematics of the overall set-up and assembled the experimental platform.

Dumitru-Cristian Trancă obtained in 2013 a BSc degree in Computer Science at the Faculty of Automatic Control and Computers, UPB, with a research project entitled *LiveVitals – A portable medical system for patient telemonitoring* under the supervision of Prof. Dr. Răzvan Victor Rughiniș. The results of his work have been published at 2013 RoEduNet International Conference 12th Edition: Networking in Education and Research. In 2015, Cristian received his MSc degree in Computer Science at the Faculty of Automatic Control and Computers, UPB. During his MSc, he studied through Erasmus EUROWEB+ student exchange programme for 10 months at the Faculty of Electronics, University of Nis, Serbia, where he finalised his thesis entitled *BikeAngel – GPS Mobile tracking system with GPRS/GSM communication system*, being presented at both universities. He pursued his Doctoral studies in the field of Computer Science under de supervision of Prof. Dr. Răzvan Rughiniș, with the thesis entitled *Optimizations in Industrial Internet of Things.*
Within his work period as a Research Engineer in Computers at Enevo Group he was the head of hardware development team within project MediLU150 and LumPowerMeasure, under the scientific coordination of Prof. Dr. Mihail-Lucian Pascu.
Within the DropTES 2018 project, Cristian was responsible with the automation and synchronisation of the experimental set-up, involving the design and manufacturing of electronic control boards.

Ioana-Simona Stroescu obtained a BSc degree in Biochemistry from the Faculty of Biology, UB, in 2018. Her studies involved epidemiology, control of bacterial, fungal and viral infections, development of new antimicrobial strategies as well as the identification of microorganisms by microbiological methods. Simona undertook UV-Vis-NIR absorption and FTIR spectroscopy as well as microbiology and encapsulating techniques of nanoparticles in order to test the effect of drug emission on cancer cells. She was member of the biochemistry group at the ROMAR Medical Center, specialised in medical analysis. Currently, Simona is working as Assistant Research Scientist at the LSO and commenced her MSc studies under the supervision of Prof. Dr. Mihail-Lucian Pascu.
Within the DropTES 2018 project, she prepared the medicine solutions, carrying out preliminary investigations on their spectroscopic properties.

One must acknowledge the support of **Dr. -Ing. Thorben Könemann**, the Deputy Scientific Director of the ZARM Drop Tower Operation and Service Company, throughout the constructive collaboration, involving the revision of the EPRs and technical consulting. During the experiment integration and campaign on site, the DropTES 2018 team has been supported by a dedicated team of two drop tower engineers, by **Dipl. -Ing. Fred Oetken**, professional in electrical, and **Dipl. -Ing. Jan Siemer**, professional in mechanical engineering.

Another important collaboration that must be mentioned was between the DropTES 2018 team and **Ayami Kojima**, from the Space Applications Section (SAS) of UNOOSA, helping the team with the logistic part of the project.

The multidisciplinary background of the team provided an asset to the success of the project and may lead to innovative results in the use of micro- and optofluidics in space science. Figure 1 shows the entire team and the student team members after the last experiment.

Figure 1. The DropTES 2018 team with their experiment capsule at the deceleration unit.

1. Introduction

Throughout time, exploration with its promise of ground-breaking discoveries has always been one of the most inherent and defining trait of mankind. As space missions have gained momentum and became more frequent with the advancement of explorations, potentially dreadful challenges including microbial infections onboard space vehicles came into light.

As early as Apollo and Skylab missions, altered and weakened immune responses of returning astronauts were identified, thus potentially compromising their defence against infections during space voyages [1-3]. Human habitation in confined space – whether permanent or temporary – is accompanied by co-habitation with microbes [4]. Especially where air, water, food and waste are recycled, the development of pathogens onboard spacecraft may constitute a major risk for health of crew members and hardware safety, consequently compromising the success of the mission. Due to continuous evolution of drug resistance against pathogenic infections, both on Earth and in outer space, new strategies for innovative treatment methods are required when executing long-lasting space missions.

The alternative solution proposed for DropTES 2018 project consists in utilising multifunctional drugs and an unconventional method to make them acquire antimicrobial properties by exposure to UV laser radiation. The concept of optically induced structure modification of existing medicines leads to transformation of the parent-compound into new and more efficient photoproducts that may have – either individually or in mixture – increased antimicrobial activity, compared to the unirradiated medicines [5-8]. Therefore, the use of photosensitive non-antibiotics was proposed for this project. It is known that non-antibiotics may reduce or reverse antibiotic resistance of a variety of pathogenic bacteria [9, 10], while due to their photosensitivity, they undergo modifications at molecular level once exposed to white light or to UV radiation. When subjected to white light, these medicines experience a slow process of alteration, whereas UV light speeds up the change of the initial chemical structure. Above all, an UV laser beam induces faster modifications in contrast to non-coherent UV light sources, due to its high energy and monochromaticity [5, 6]. There are two ways to modify such medicines: in bulk and in droplet using ultrapure water as solvent; the interaction may be either resonant or unresonant. Regarding resonant interaction, in droplets, the laser radiation is – partially or fully – absorbed by the medicine components and, after absorption, is followed by laser induced fluorescence (LIF) [11, 12]. When unresonant phenomena dominate droplets behaviour – the beam is not absorbed by droplet constituents – the interaction is followed by several effects, such as, among others: damped deformations and vibrations, expulsion of micro-jets that propagate with high speeds and production of micro- and nanodroplets [13, 14].

On the other hand, it has been evidenced that microgravity (µg) conditions can be associated with the evolution of microorganisms into more virulent forms [1-3, 15]. During the Microbe experiment, performed under the aegis of NASA [4], *Salmonella typhimurium* [3], *Pseudomonas aeruginosa* [16] and *Candida albicans* [17] have been examined from the point of view of their gene expression and virulence attributes. As shown in [3], *S. typhimurium* grown aboard Space Shuttle Atlantis, mission STS-115, acquired altered and enhanced virulence in comparison with identical ground controls. Actually, an entire flora of pathogens may grow in the enclosed medium of a spacecraft, as it has occurred on the orbital station Mir during its 15 years of operation, when a total of 234 species and 65 genes of bacteria and fungi were identified onboard [18]. Additionally, 20 bacterial isolates were found in drinking and recycled water on Mir [19]. *Pseudomonas* has been once regarded as the source of infection of astronauts during the Apollo era, being mainly detected in the water system of spacecraft [16, 20].

Consequently, DropTES 2018 project aimed to investigate – beside the irradiation/modification processes of non-antibiotics under the effect of µg – the interactions of such medicines with particular target surfaces which are present onboard space vehicles. The proposed technique in order to explore these interactions consists in wettability studies by determining the time evolution of contact angle and wetted diameter of droplets with different surfaces. Wetting processes play a crucial role in biomedical treatments and may serve as a promising tool in developing new drug delivery systems for future space medicine applications.

A phenothiazine drug, declared as psychotherapeutic agent, has been considered for experiments within DropTES 2018. Within the project, chlorpromazine (CPZ) was exposed to a 375 nm pulsed laser radiation.

The selection criteria of this wavelength were based on two factors: (i) both, extraterrestrial solar UV radiation and the UV radiation reaching the surface of the Earth (containing the UVA radiation, ranging between 320-400 nm) [21] and (ii) the absorption peaks at 254 and 306 nm of CPZ (at 0.2 mg/mL) [22], respectively.

Phenothiazines can be considered as multifunctional medicines [5-8]; normally, they are utilised to treat mental disorders, anxiety, nausea, vomiting, migraine, insomnia and hiccough [23, 24], but after laser irradiation, aqueous solutions of phenothiazines generate photoproducts with increased antibacterial and/or antifungal activity [25]. It has to be mentioned that the direct clinical application of laser modified phenothiazines has not yet been implemented.

As early as 1969, medical kits containing antibiotics, antinauseants, painkillers, etc. were carried on Apollo 11. Most of them are nowadays part of the current medical kits and are taken by crews to fight diseases, possibly encountered during their missions. Although there is evidence that pharmacokinetics and pharmacodynamics suffer modifications in space flight environment, thus altering drug efficacy as well as the severity of side effects, relatively little is known about μg-associated changes to these parameters. Previous anecdotal reports have shown that crew members have experienced sometimes absence or great attenuation of such side effects.

In order to better understand the behaviour of droplets in extraterrestrial conditions from the point of view of their micro- and optofluidic properties, the DropTES 2018 project aimed to bring a new insight into the impact of diminished g conditions on medicine droplets, their real-time modification *via* UV laser pulses as well as on the wettability of target surfaces once the droplets get in contact with them. Therefore, the following scientific objectives of the project have been proposed:

- exploring the effect of μg on the shape of unirradiated and laser irradiated medicine pendant droplets;
- exploring the evolution of laser induced fluorescence (LIF) emitted in real time by medicine pendant droplets in μg conditions;
- determining the surface tension (ST) of unirradiated and laser irradiated medicine pendant droplets in μg;
- exploring the effect of μg on the shape of unirradiated and laser irradiated medicine sessile droplets on aluminium surfaces;
- determining contact angle (CA) and wetted diameter (WD) of unirradiated and laser irradiated medicine sessile droplets in μg.

A comparative study between the effects of micro- and terrestrial gravitational conditions on the above-mentioned parameters represented another target of the project.

2. Materials and methods

2.1. Medicine solutions

Phenothiazine solutions proposed for DropTES 2018 contain CPZ as solute, purchased from Sigma-Aldrich in hydrochloride powder form at a purity > 98%. Milli-Q Millipore ultrapure water (UPW) is utilised as solvent, medicine solutions being prepared at 20 mg/mL concentration and stored at 2-5 ℃ in a dark environment.

Electronic structure calculation software, Gaussian 09, was used to obtain the optimized geometry of the phenothiazine molecules in their fundamental state. In order to attain the respective structures, the calculation employed density functional theory (DFT) alongside the B3LYP functional and the 6-31G(d,p) basis set [26]. This basis set is known to give accurate results when dealing with small organic molecules [27]. The studies were conducted using water as a solvent, being achieved by using the Integral Equation Formalism Polarizable Continuum Model (IEFPCM), a model that places the solute in a cavity within the solvent reaction field. This method creates the solute cavity via a set of overlapping spheres [28]. The program computes the energy within the solution by making the solvent reaction field self-consistent with the solute electrostatic potential, the latter being generated from the computed electron density with the specified model chemistry [29]. The images of the optimized structures, shown in Figure 2, were obtained using GaussView 5.0 visualization software [30].

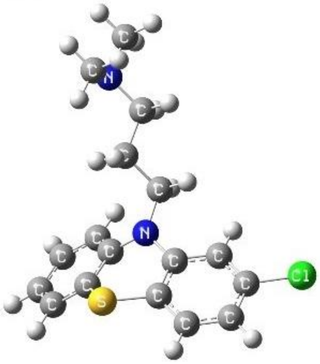


Figure 2. 3D representation of CPZ molecule with optimised geometry [22, 26].

It has to be specified that due to stability and photosensitivity of such solutions, the DropTES 2018 team prepared the unirradiated medicine solutions on site, at Bremen Drop Tower.

2.2. Medicine solutions characterisation

Prior to laser exposure and DropTES 2018 campaign, phenothiazine solutions have been characterised by different techniques performed at laboratory room temperature (20–25 °C), as mentioned below.

The pH of unirradiated solutions was measured utilising a Schott Instruments Lab 860 pH-meter.

Absorption spectra of unexposed phenothiazine solutions has been recorded between 200 and 1000 nm by a PerkinElmer Lambda 950 UV-Vis-NIR spectrophotometer using 1 and 10 mm optical path quartz cuvettes.

FTIR spectra of medicine solutions were recorded with a Thermo Scientific Nicolet iS50 spectrometer in the range of 400-4000 cm^{-1}, at a 4 cm^{-1} resolution. Due to high absorption presented by water in the IR region, 20 μL drops of aqueous phenothiazine solutions were placed and dried on a thallium bromo-iodide, KRS-5, support. Its background was subtracted from all the spectra, thus obtaining only qualitative results [31].

The refractive index of medicine solutions was determined by a Carl Zeiss 701878 Abbe refractometer.

ST and visco-elasticity measurements on pendant droplets containing medicine solutions have been carried out using Sinterface, PAT-1 Drop and Bubble Shape Tensiometer in a protected environment conceived to avoid excessive droplet evaporation and air current influence on the measurements.

2.3. Droplet generation

2.3.1. Droplet injection

Within the DropTES 2018 campaign, a remotely controlled Cole-Parmer Programmable Syringe Pump 75900-00 has been implemented to generate phenothiazine droplets on the tip of a Hamilton Kel-F Hub blunt, electropolished capillary, placed in a 100 μL glass Hamilton Gastight Syringe with Luer Tip, by a native dispersing program.

2.3.2. Droplet illumination

Droplets have been illuminated by a red LED with adjustable intensity, provided by ZARM.

2.3.3. Droplet visualisation

Within the DropTES 2018 project, a rugged Vision Research Phantom Miro 3 high-speed and high g supporting camera was utilised for video data acquisition, using the Phantom Camera Control Application (PCC) 2.6 software. Its maximum speed at full resolution of 800x600 pixels is 1200 frames/s, while at a reduced resolution of 32x16 pixels is 111111 frames/s. The camera was previously implemented in Spin Your Thesis! 2015 campaign, being subjected to the maximum 20 g hypergravity conditions available at the Large Diameter Centrifuge of the European Space Research and Technology Centre (ESTEC), European Space Agency (ESA). Within DropTES 2018, a 640x320 pixels resolution has been used with 2000 frames/s recording speed, the time between 2 consecutive frames being 500 μs. The shutter speed of the camera can be as low as 2 μs, thus providing high quality images for motion analysis by eliminating the blur. The 17.6x13.2 mm size CMOS sensor is characterized by 22 μm pixel size and 12-bit depth.

The objective used in the project associated to this camera was a Nikon AF-S Micro Nikkor 60 mm f/2.8G ED coupled with a Bower C-mount adaptor for Nikon lens.

2.4. Laser exposure

Phenothiazine solutions has been exposed to 375 nm continuous wave (CW) laser radiation, emitted by an ALPHALAS PICOPOWER-LD-375-50 diode laser with a PLDD-50M driver.

Preliminary irradiation experiments have been performed by the DropTES team and results on LIF measurements are described in Section 4.1. One should mention that similar experiments have been reported by the team leader and his co-workers using a Continuum, Surelite II pulsed Nd:YAG laser emitting at the 4th (266 nm) and 3rd (355 nm) harmonics of the fundamental beam (1064 nm) and delivering pulses of 3 mJ average energy with a full width at half maximum (FWHM) pulse duration of 6 ns at a repetition rate of 10 Hz [32]. Droplets of CPZ solution at 10 mg/mL concentration have been exposed to such laser radiation in a configuration where the laser beam was not focused but quasi-parallel. In order to obtain such design, a 150 mm focal length lens has been implemented. Taking into account the 5.6 mm beam cross-section on the lens, the droplet was positioned at a distance of 220 mm from the lens on the propagation axis of the beam, thus almost fully covering the droplet cross-section, considering spherical droplets with 2.67 mm diameter at 10 μL volume. Real time monitoring of the beam energy was carried out by a Gentec-EO powermeter, alongside a Thorlabs beam splitter placed in the beam path. The 524 mW/ cm^2 average power density was calculated considering the average laser power incident on the exposed circular area 0.056 cm^2 of the droplet. Droplets were exposed to 266 and 355 nm laser beams, respectively, for time intervals ranging from 10 s to 5 min [32].

Within the DropTES 2018 set-up, due to the preservation of the laser beam diameter over the desired distance (beam divergence < 3 mrad), an additional lens for collimation was no longer required. The operating parameters of the laser system, during the preliminary tests, have been set to CW regime. One has to consider the fact that within drop operation mode the μg experiment time will be 4.54 s extracting the 0.2 s time interval when the μg quality is not within the measurement range [33], thus limiting the interaction time of laser beam with droplets to, at most, 3 s. Therefore, CW regime was selected, in order to be able to induce structural changes within the droplet content within the given time interval.

2.4.1. LIF measurements

The formation of photoproducts in a droplet was traced by recording the emitted LIF spectra in real time, utilising an Ocean Optics HR 4000CG-UV-NIR portable spectrometer with a < 0.5 nm optical resolution (FWHM), wavelength range of 200-1100 nm and signal-to-noise ratio 300:1 (at full signal). A Thorlabs optical fibre, with a 1500 μm core, 0.39 numerical aperture and 300-1200 nm operating wavelength range was used to collect the signal from the droplet.

The DropTES 2018 team proposed to find out the spectral and temporal evolution of such LIF signals in μg conditions. The collected LIF signal at μg has been compared with the one obtained in terrestrial conditions. It is expected that the double exposure – μg and laser – leads to different molecular modifications inside the medicine droplet from those studied in 1 g conditions. This is the reason why irradiation of phenothiazine droplets during free fall conditions at the Bremen Drop Tower has been proposed. Since in μg environment there is no sedimentation, one may find in fluids a homogeneous particle distribution [34]. Therefore, such a different distribution of molecules inside a medicine droplet, at reduced gravitational environment compared to the terrestrial one, could be detected by real time LIF spectra collection.

2.5. Target surfaces

The target surface used in μg conditions consisted in smooth, impermeable aluminium surface, processed from raw material by standard polishing procedures.

2.5.1. CA and WD measurements

The wetting properties of the aluminium target surface has been investigated by measuring CA and WD formed by unexposed and laser exposed medicine solutions. Data regarding UPW has also be determined, playing the role of the reference solvent. Measurements taken at liquid-air interface of different droplets in contact with the solid surface would yield different wettability data.

Krüss Advance software has been utilised for CA and WD determination. The software implements grayscale images of droplet interaction with target surfaces, exported from recorded movies, in order to define contact lines and contours of sessile drops, thus obtaining the desired parameters.

2.6. μg conditions

Four experiments were conducted in dropping mode at the Bremen Drop Tower. Having a height of 146 m and diameter of 8 m, the tower provides 10^{-6} g μg conditions [33]. With a height of 120 m and diameter of 3.5 m, the drop tube inside the drop tower is almost air free for the duration of the experiments thanks to 18 high performance pumps. Due to the vacuum, the air drag is so low that the Bremen Drop Tower can provide one of the highest-quality of μg environment for 4.74 s, in some aspects even better than on the International Space Station (ISS) [35].

Besides the high-quality of μg, another advantage of using the Bremen Drop Tower consisted in the fact that it allows the use of large set-ups in developing experimental tests.

3. Experimental set-up and procedure

Within the DropTES 2018 project, microvolumetric droplets were generated in µg conditions. The syringe pump, described at Subsection 2.3.1, has been upgraded in order to adopt 3 syringes instead of one, thus enabling the simultaneous generation of 3 pendant droplets (UPW, unirradiated CPZ and another unirradiated CPZ which has been exposed in real time to UV laser beam), as presented in Figure 3, broadening the statistics of measurements within the DropTES 2018 campaign.

Droplets were generated in the immediate proximity of the target surface, however without external force exerted on them over a short time, at ms order of magnitude; the droplets would have remained attached to the capillary in µg environment and would have not got in contact with the target. Therefore, the following method has been considered to facilitate detachment of droplets from capillary at the desired volume and time moment: translating the target surface up and then down by using a stepper motor provided by ZARM.

Another method, which would have provided certain contact of droplets with the target surface, consists in the generation of sessile droplets – instead of pendant ones – through an orifice made into the target surface [36, 37]. The drawback of this technique is that it does not enable to determine accurately CA and WD.

Droplet generation, behaviour, exposure to laser beam and interaction with targets was visualised and recorded with a high-speed camera. Videos have been used for post-analysis to determine CA and WD. In order to obtain a refined silhouette of medicine droplets, the backlit illumination technique was employed, consisting in a diffuse illuminator placed opposite to the camera. This technique provided a dark and sharp image of the drop on a white background, hence facilitating detection of contact line alongside the contour of the sessile drop by utilising a drop shape analyser software in order to study the wetting phenomena.

Figure 3. Pendant droplets of UPW, unexposed and real time laser exposed CPZ solutions for µg studies at the Bremen Drop Tower. Three syringes for each medicine has been used.

It has to be mentioned that a proper field of view had to be selected keeping a balance between suitable resolution and high frame rate, in order to obtain the desired visualisation of 3 droplets, one next to another.

A special feature of DropTES 2018 set-up consisted in a UV laser subsystem. The exposure time intervals of droplets lasted ≈ 3 s. LIF spectra evolution within this interval has been recorded by the portable spectrometer via an optical fibre, specified at Subsection 2.4.1.

Since degradation time of parental medicine compound and new photoproducts formation greatly depend on the average power density, the average incident laser beam power and the exposed area are crucial parameters, needed to be established. In previous experiments, employing a solid-state laser emitting at 355 nm, a 10 µL droplet has been exposed [32]. Due to the relatively low average power of the laser diode, the volume of the generated droplet had to be decreased in order to obtain a similar average power density. The beam power of the utilised laser was 46 mW emitted in CW regime.

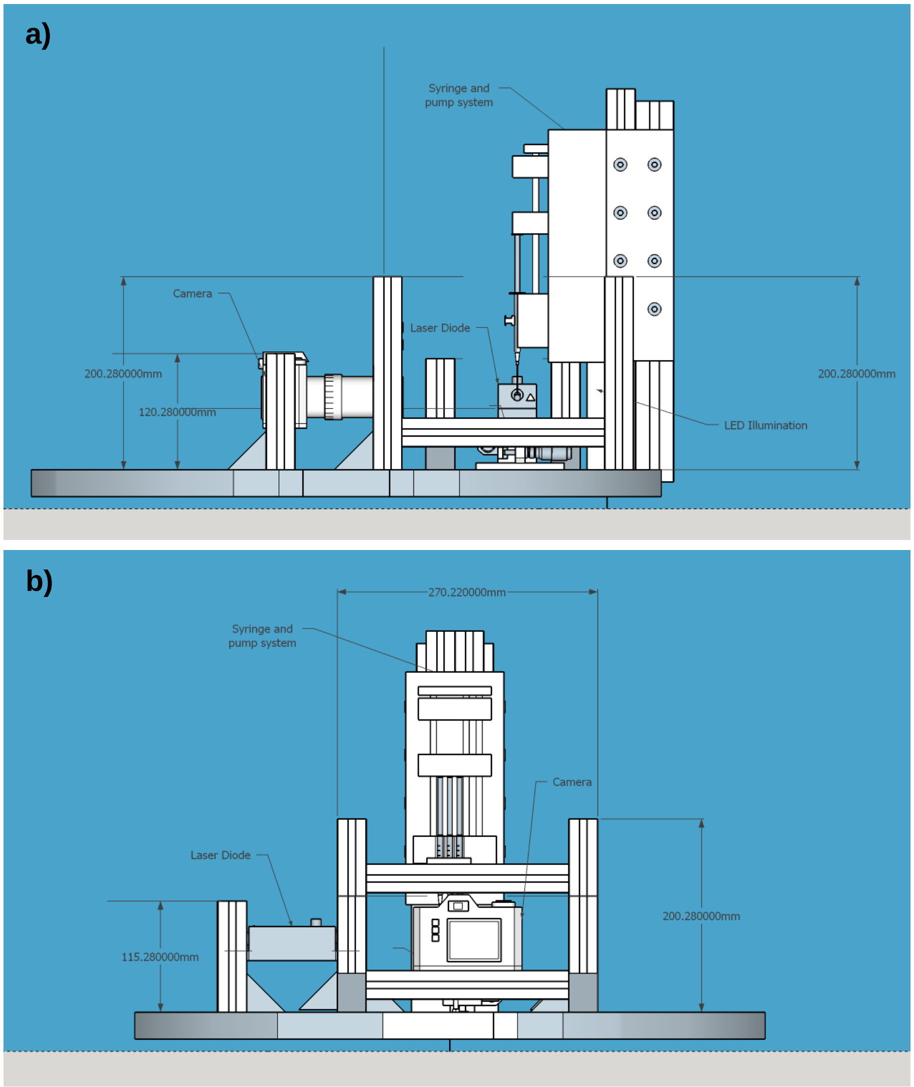
Since wetting processes under terrestrial and hypergravity conditions are fast, with a max. timescale up to 250 ms [22], the remaining time after the ≈ 3 s irradiation was long enough to study the interaction of droplets with target surfaces. Even if a longer exposure to μg environment would have been preferable, the DropTES 2018 set-up should have not transit through hypergravity at launch. The capillaries would have most certainly ejected their content and the experiment would have entered in μg without the testing liquids. Another vulnerable element would have been the laser exposure set-up, possibly getting misaligned due to the exerted high g levels before the experiment.

In Table 1 the following schedule has been considered for the DropTES 2018 campaign:
3 droplets/experiment x 1 experiment/day x 4 days of experiments/week = 12 measurements.

Table 1. Work plan of DropTES 2018 project at Bremen Drop Tower.

Day	Experiment	Medicine	Concentration	Volume	Target surface	No. of measurements
19-23 November 2018	Set-up integration and ground testing					
26th November 2018	#1	CPZ	20 mg/mL	7 μL	untreated Al	3
27th November 2018	#1	CPZ	20 mg/mL	7 μL	untreated Al	3
28th November 2018	#1	CPZ	20 mg/mL	7 μL	untreated Al	3
29th November 2018	#1	CPZ	20 mg/mL	7 μL	untreated Al	3
30th November 2018	-					
Total No. of measurements						**3x1x4=12**

The technical representation of capsule payload from different observation points is illustrated in Figure 4.



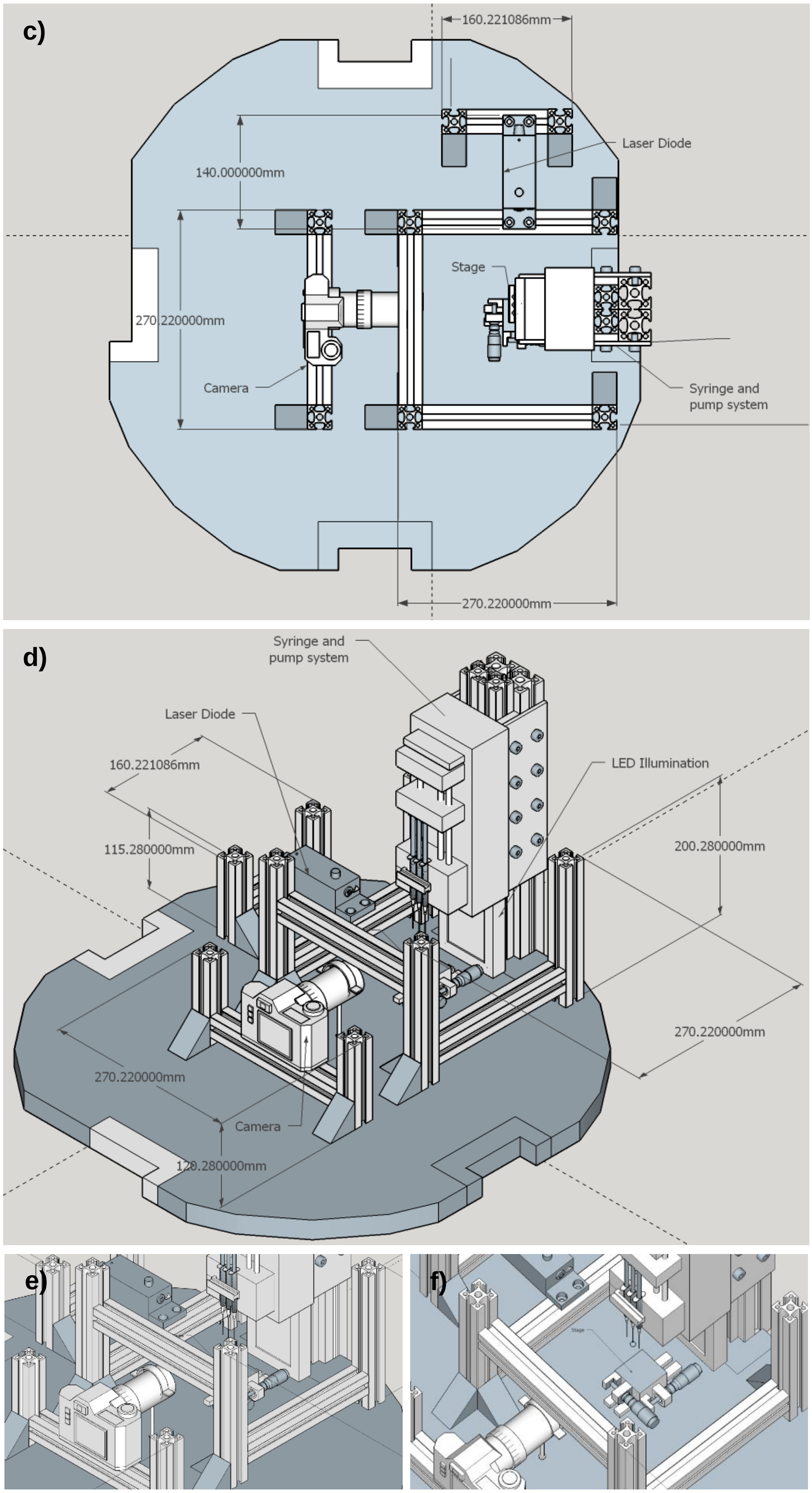


Figure 4. Capsule payload from a) front, b) side, c) top and d)-f) isometric view.

The DropTES 2018 set-up integrated inside the ZARM drop capsule is displayed in Figure 5. The left picture shows an overview, while the right one illustrates a close-up regarding the three droplets on the aluminium surface detached from the Teflon coated capillaries after the irradiation procedure has took place.

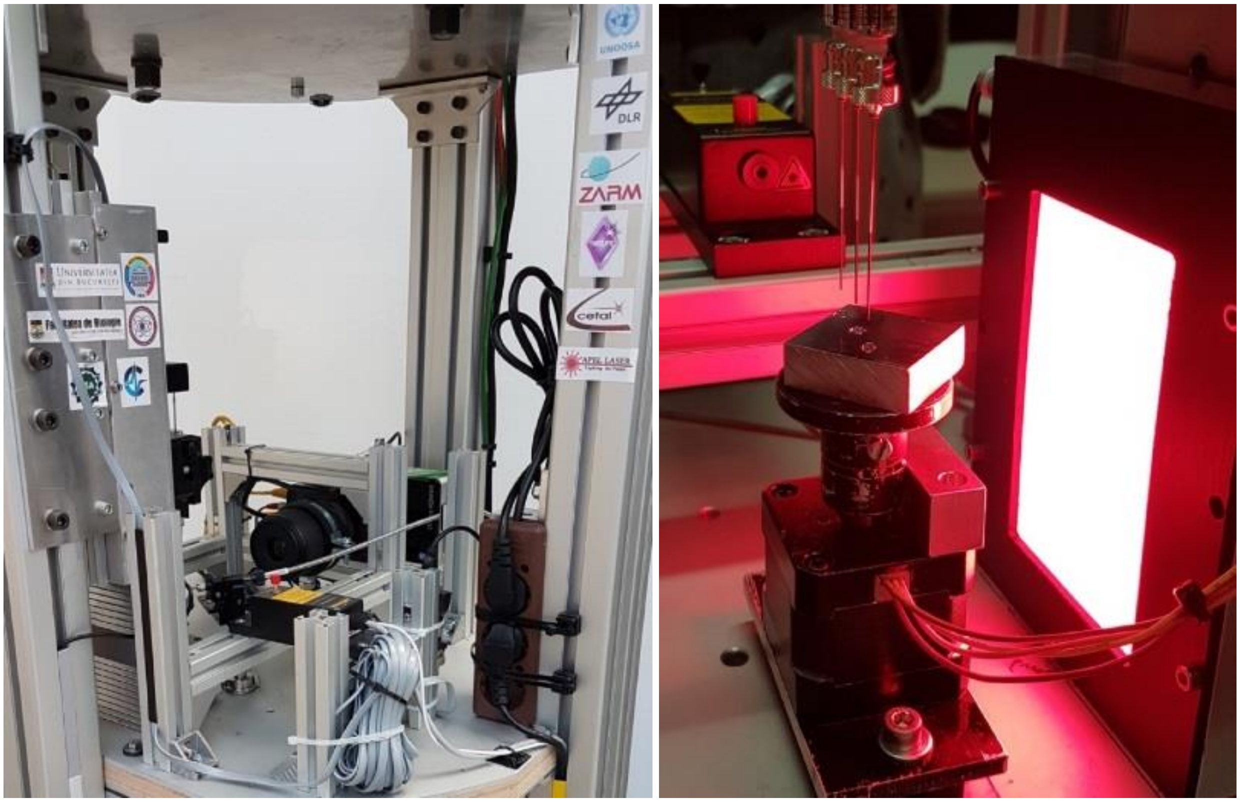


Figure 5. The DropTES 2018 final set-up integrated inside the ZARM drop capsule.

3.1. Automation system architecture

The DropTES 2018 experimental set-up consisted of the following devices:

- Intel NUC x86 based Mini PC (Maguay OfficePower NUC);
- configurable digital I/O data acquisition board (National Instruments USB-6501 24-Channel, 8.5 mA, digital I/O device);
- ATmega328 based microcontroller development platform (Arduino Uno);
- signal conditioning circuitry (custom build);
- 24VDC to 230VAC DC to AC inverter;
- laser control unit;
- injection pump with internal control unit;
- spectrometer;
- high-speed camera;
- multiple DC to DC converters for powering the mini PC, the injection pump unit and the signal conditioning board.

In Figure 6 it is presented the conceptual high-level architecture of the automation system. The system design allowed a complete automated control of the laser, translation table, injection pump and high-speed camera. The high-speed camera and the laser control unit were powered using the DC to AC inverter. The Intel NUC mini PC, the injection pump and the Arduino Uno development board were powered through separate DC to DC converters, while the configurable I/O data acquisition board, the spectrometer and the signal conditioning board have been powered through USB by the mini PC unit.

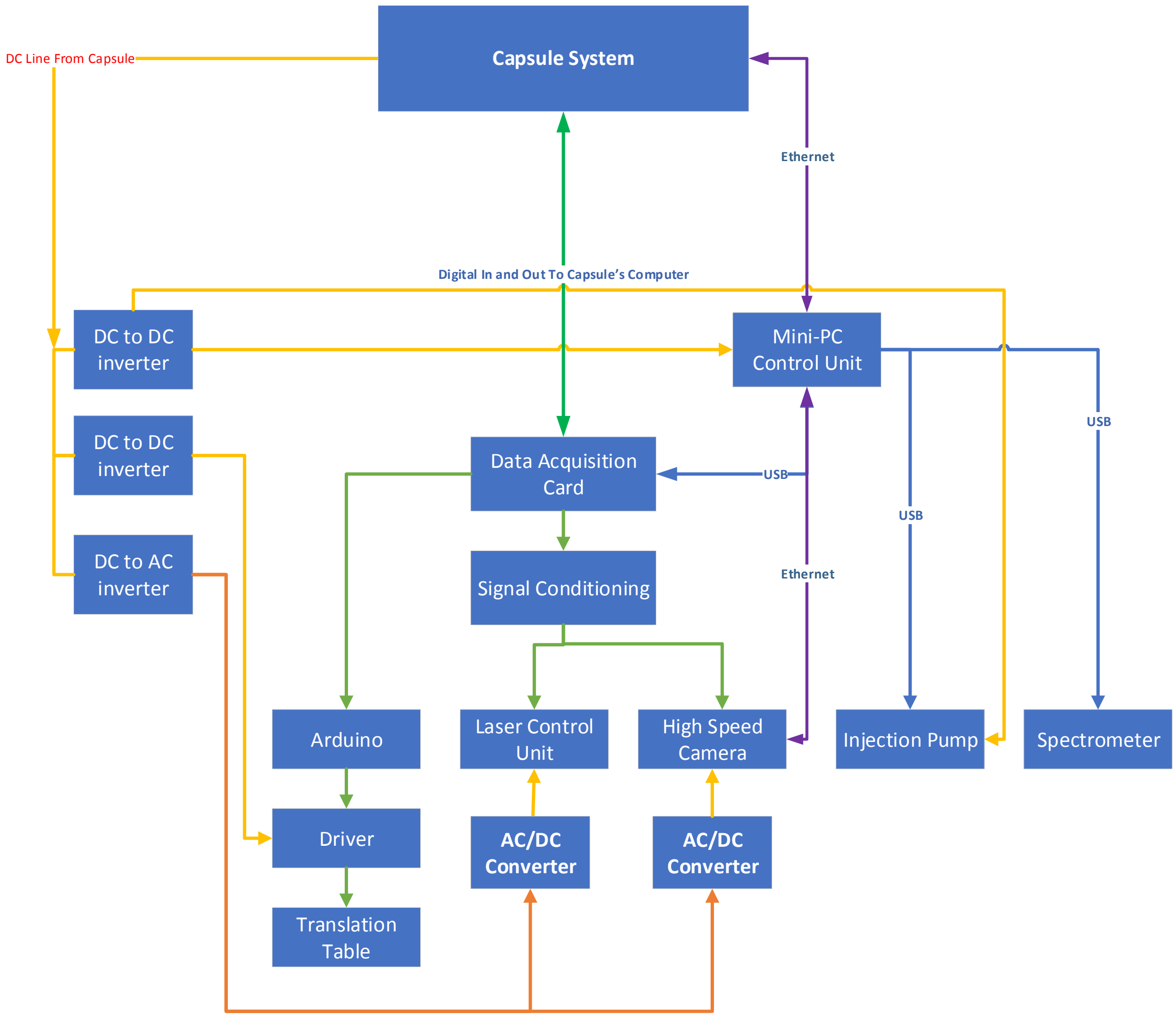


Figure 6. System architecture diagram of the DropTES 2018 project.

The mini PC was the main control unit for the scientific experiment running all the necessary software that allowed the automation of the experimental procedure. Besides the automation procedures, the mini PC recorded data from the spectrometer, from the camera and logged each event with its timestamp. The mini PC directly controlled the spectrometer, the data acquisition board, and the injection pump through USB 2.0 interfaces (one for each device).

The configurable I/O board was responsible for controlling the laser unit (turning the lased ON and OFF), triggering the high-speed camera, triggering the movement of the translation platform and interfacing with the capsule's main computer through a set of digital inputs and outputs.

Since the configurable I/O board was software timed, and the translation platform (based on a stepper motor with an included driver) needed precise timing that could not be achieved using the configurable I/O board, we have used an ATmega328 based Arduino Uno microcontroller development board. Since the microcontroller can obtain a real-time execution of the algorithm, we used it to precisely control the rapid movement of the translation platform. The Arduino development board role was to execute a fast up – down translation of the table containing the target surface in order to detach the droplets on it. The movement controlled by the Arduino was triggered through the configurable I/O board.

The signal conditioning board was used to electrically isolate the trigger signals from the I/O board to the camera and to the laser unit, insuring a better noise immunity and eliminating the possibility of logic hazard (random triggering of the laser or the camera) behaviour.

The automation systems communicated with the control room via ethernet (remote connection) and with the capsule's computer via two digital lines. One digital line was used to transmit a signal to the capsule's computer after the initialization sequence has been finished, and another to transmit a signal from the capsule's computer to the mini PC that controlled the experiment when the capsule was detached from the support and the experiment began.

3.2. Hardware circuit of the signal conditioning unit

In Figure 7 the electrical schematic of the signal conditioning unit is illustrated. One can observe from the schematic that all the output signals have been electrically isolated using transistor output optocouplers. The system has been designed to control the laser control unit and the high-speed camera using open-collector topology. To turn ON or OFF the laser or to trigger the camera, through the data acquisition card, an activation signal was sent on one output (software mapped for each connected device).

Since the outputs of the data acquisition board had a limited current output, an integrated array of Darlington transistors (ULN2003) was used to activate the optocouplers. All the power needed for the optocouplers has been provided directly from the 5 V power line that can source up to 200 mA.

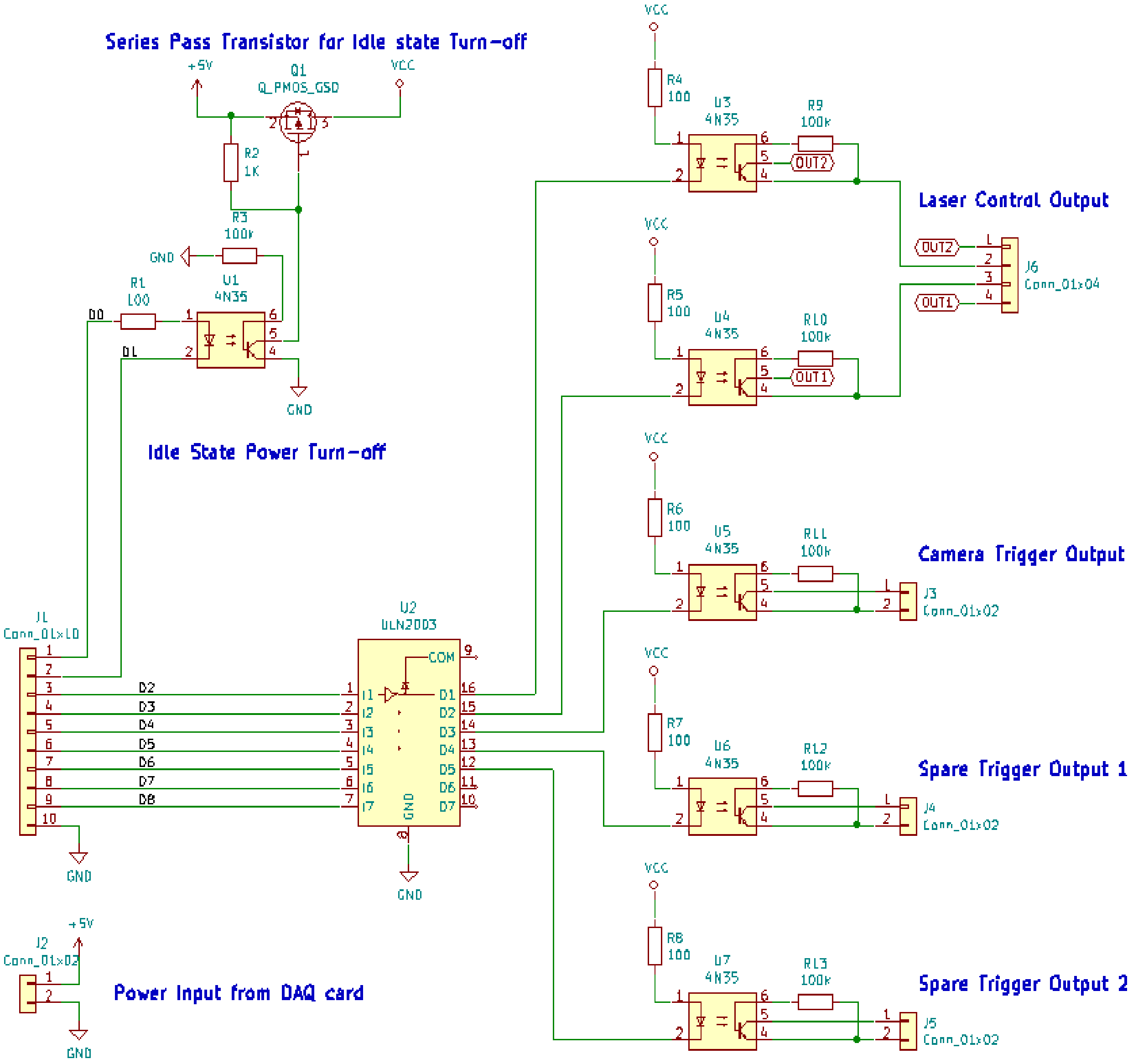


Figure 7. Electronic schematic of the signal conditioning unit.

Because of the internal pull-up resistors that output a weak logic high state in the initial power-on state or after a restart of the data link (USB), the data acquisition board was implemented using U1 and Q1 a XOR-like function (electrical interlock that prevented logic hazards and random triggering of the laser and/or camera).

This separate circuit allowed the activation of the optocouplers only if D0 output a logic high signal and D1 a logic low signal, thus avoiding hazardous turning ON of the laser if anything were to happen with the data link during the experiments.

The board 2 provided the spare outputs that served to control other devices.

3.3. Software architecture

The automation software control has been implemented using LabView programming language. The software, displayed in Figure 8, implemented the Finite State Machine (FSM).

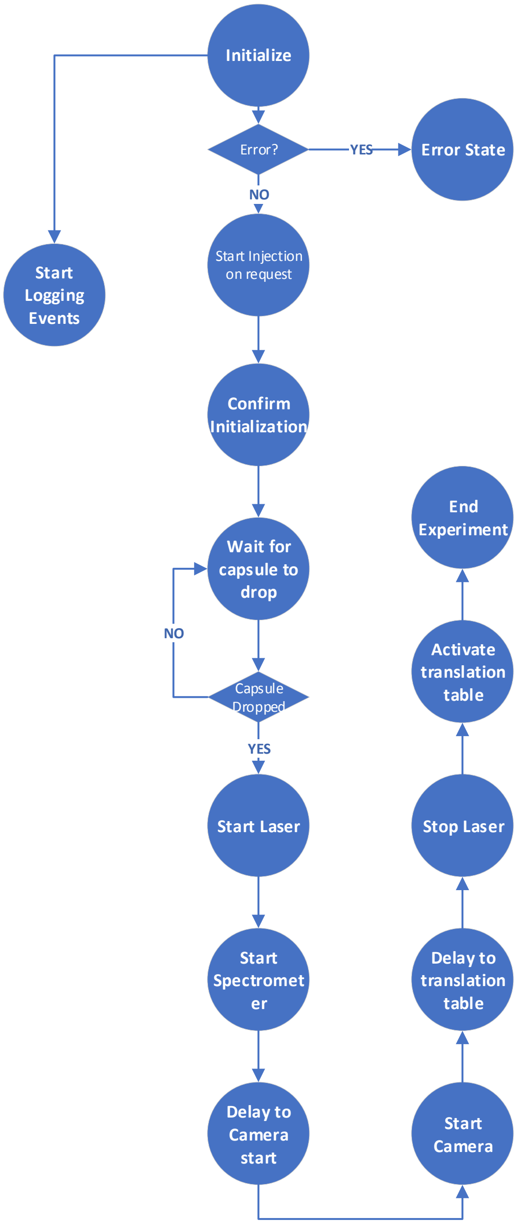


Figure 8. Finite State Machine.

The FSM was designed so that any other intermediate states could be added later on and the order to be easily modified.

The states have been implemented as follows:

- **Initialize**
    - The data acquisition device was initialised and all outputs have been correspondingly set, so that optocouplers could be easily initiated.
    - The spectrometer was interrogated and initial configuration set.
    - The injection system was initialised and the response of the injection pump verified.
    - If all initialization and testing of the devices yielded no errors, a confirmation signal was sent to the capsule’s computer; else, the system entered an error state and remotely restarted.
    - If the initialization was successful, the pumps were activated.

    The process was remotely observed from the control room. When it was assured that the droplets have been generated correctly (the procedure was enabled by pressing the **Generate Active** button), after pressing the **START** button, it was given the signal to the main system (µg request **OK**) and the capsule released (and the **Microgravity Started** indicator lighted up).
- **Wait for drop:**
    - The mini PC algorithm waited for the capsule to be released and the signal to be generated.
- **Start Laser**
    - When the capsule was dropped, the laser started.
- **Start Spectrometer**
    - Immediately after the laser started, the spectrometer also started, and continuously recorded the data.
- **Delay to Camera Start (2.2 seconds)**
    - The algorithm waited for a specific amount of time after the previous state until the camera was triggered.
- **Start Camera**
    - The camera (previously set to record with corresponding parameters) was hardware triggered to start recording.
- **Delay to translation table**
    - After triggering the camera, the system waited for a configured time interval. In this interval the experiment began in µg.
- **Stop Laser**
    - At this moment sufficient time has passed, and capsule approached ground;
    - The laser was stopped (turned OFF).
- **Activate translation table**
    - The translation table was activated, and the droplets have been detached from the needles.
- **End Experiment**
    - All of the data was saved, and the temporary memory used was freed.

In Figure 9 the graphical interface of the application that implemented the control algorithm for the experiment is presented. The current state and the evolution of the experiment have been indicated in real-time during the experiment.

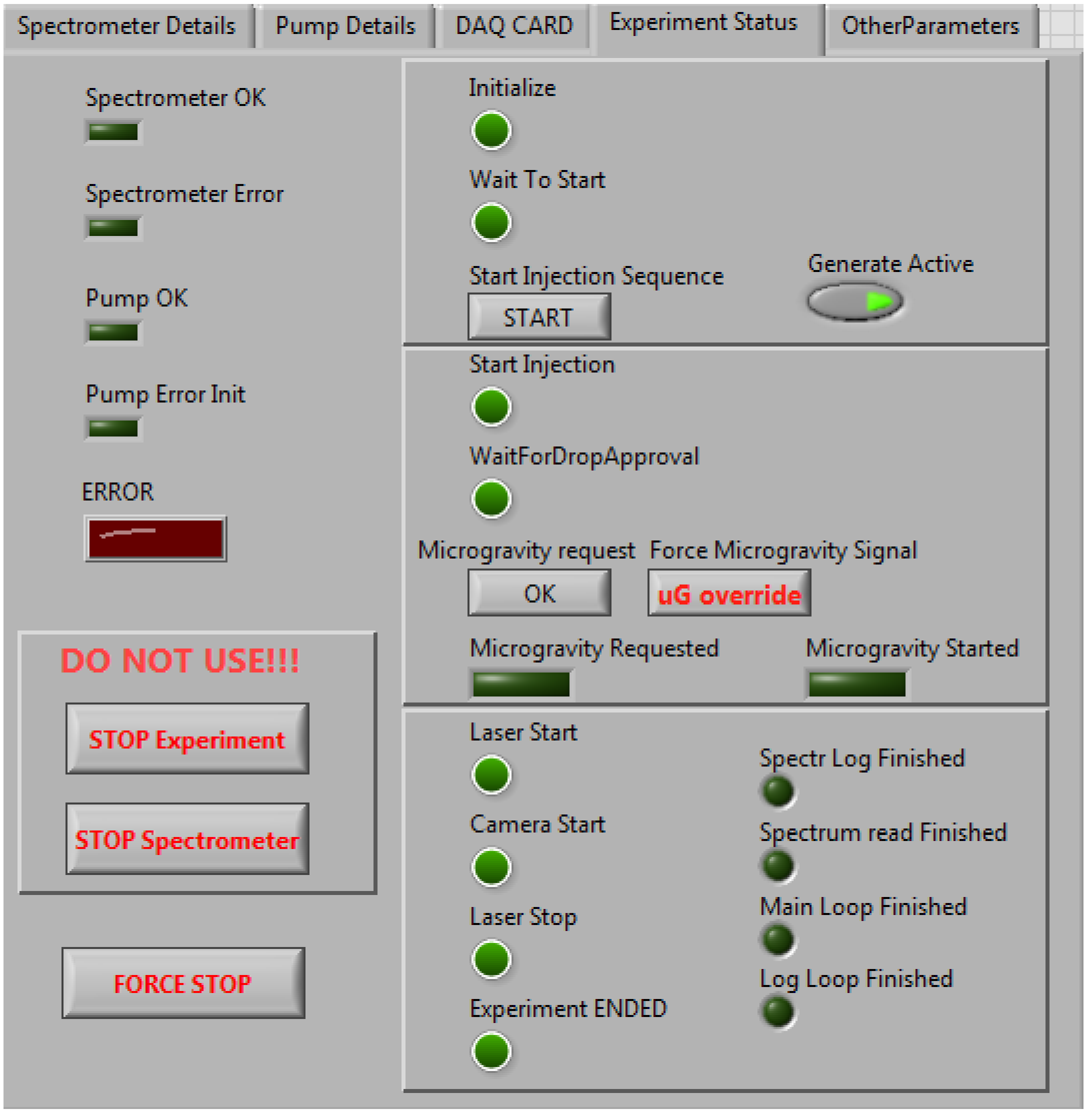


Figure 9. Application graphical interface.

For safety and fall-back measures, to ensure a graceful degradation of the system in case of error, override buttons and force STOP buttons have been included. These buttons were intended to be used in case of failure conditions (did not occur in any of the experiments).

4. Results and discussions

4.1. Pre-analysis

The pH of the unirradiated CPZ was 4.97. The pH evolution of laser irradiated phenothiazine solutions has been reported in [22], where an exponential pH decrease was observed with the increase of the exposure time (by Nd:YAG @ 266 nm).

Absorption spectra of CPZ solutions at different concentrations have been recorded in quartz cuvettes having 1 and 10 mm optical paths, respectively. At 10 and 20 mg/mL, below 400 nm, the absorption spectra are saturated [5], for this reason solution at 0.2 mg/mL has been also proposed for measurement, results being in agreement with [6] and displayed in Figure 10.

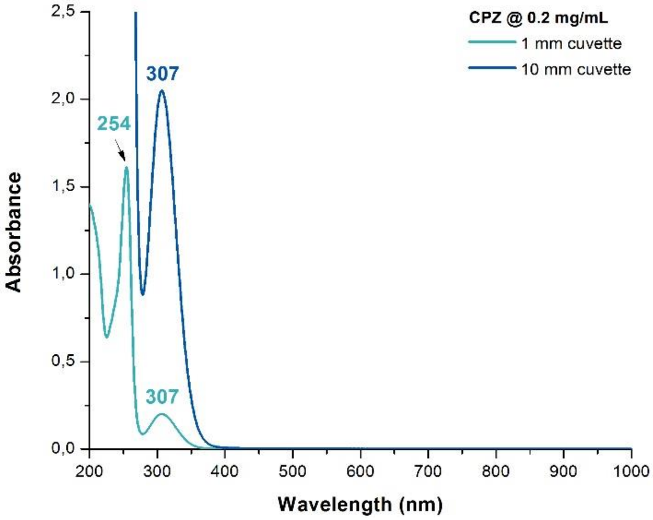


Figure 10. Absorption spectra of unirradiated CPZ solution at 0.2 mg/mL in cuvettes with different optical paths.

Two absorbance peaks, at 254 nm and 307 nm, may be observed at 0.2 mg/mL, the 307 nm probably resulting due to a n–π* transition [8].

Even if at 20 mg/mL absorption spectra are saturated, this is the desired concentration for the DropTES 2018 project, since according to [6] the use of higher concentration of CPZ in water leads to an increased number of generated photoproducts.

FTIR spectra have been recorded for the 3 concentrations of CPZ solution, illustrated in Figure 11.

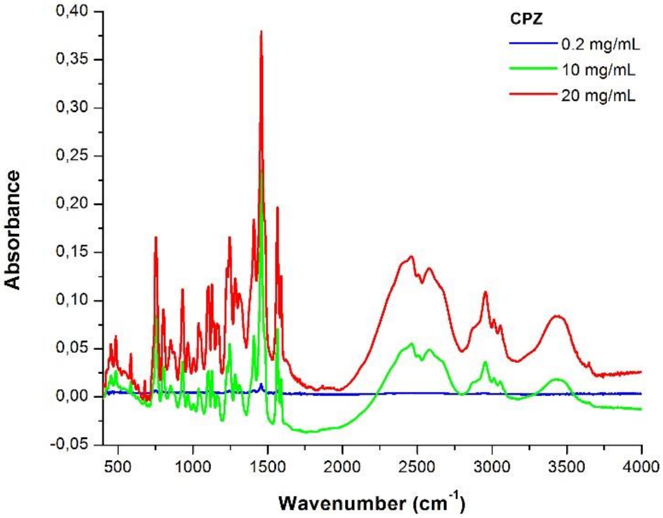


Figure 11. FTIR spectra of 0.2, 10 and 20 mg/mL unirradiated CPZ solutions.

Different characteristic vibrations of CPZ solutions have been identified and detailed in Table 2.

Table 2. Characteristic vibrations of the molecular bonds of unexposed CPZ.

Type of vibration	**Wavenumber (cm^{-1})**
=C-H sp hybridized	3152
=C-H sp^2 hybridized	3053 and 3020
=C-H sp^3 hybridized	2962
N$^+$H hydrate vibration	2672-2470
stretching vibration of the aromatic ring C=C-C	1590 and 1566
stretching vibration of C-H from $\rangle\mathrm{CH_2}$	1457
=C-H in-plane deformation vibrations of 4-adiacent H atoms of the ring system	1282
aromatic =C-H in-plane deformation vibrations-wagging	1000-1250
in-plane deformation vibrations-scissoring of C-H from ($\rangle\mathrm{N-CH_3}$)	950-1150
C-N stretching vibration	865-1180
out-of-plane bending vibration of 4-adiacent H atoms of the ring system	755
stretching vibration C-Cl	804

The refractive index of CPZ solutions has been determined for different concentrations: 1.334 for 0.2 mg/mL, 1.335 for 10 mg/mL and 1.337 for 20 mg/mL.

Real time LIF spectra could detect changes alongside dynamic ST measurements in µg conditions, exhibiting possibly different migration of newly formed photoproducts to the air-fluid interface. LIF spectra recorded under terrestrial conditions are shown in Figure 12. One may observe that after 500 ms the LIF signal increases, reaching its maximum after 1 s. CPZ at 20 mg/mL has one peak at 500 nm.

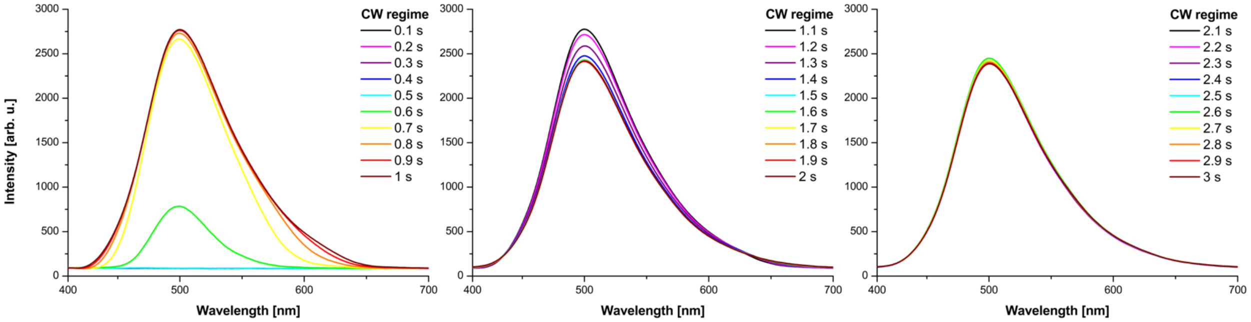


Figure 12. LIF spectra of CPZ at 20 mg/mL, irradiated 3 s with the 375 nm laser diode.

The purpose of the ST measurements was to study the surface characteristics of phenothiazine medicine droplets. Figure 13 shows the evolution of ST in time, function of concentration (UPW is exhibited as reference). Measurements have been performed at the aqueous medicine solution-air interface.

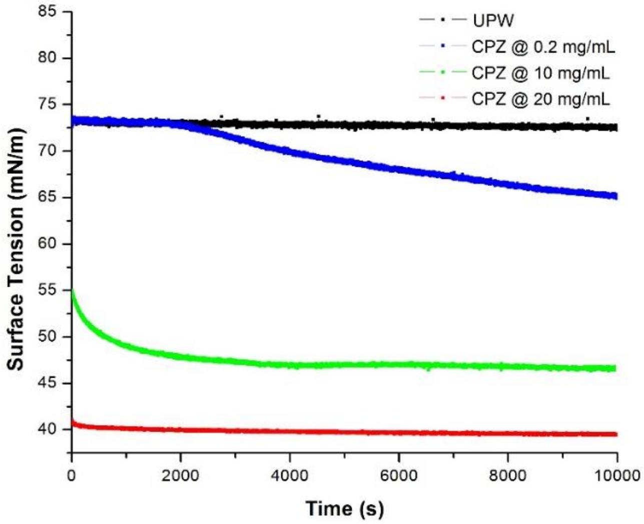


Figure 13. ST of unirradiated CPZ medicine droplets at 0.2, 10 and 20 mg/mL concentrations.

It has been evidenced that CPZ solutions exhibit reduced ST compared to water. It can also be observed that with the increase of CPZ concentration, ST values decrease. Due to their structures, phenothiazines behave as surfactants, showing lower than water ST and CA (i.e. outstanding wetting properties) [22].

In order to evaluate the rheological properties of the samples, the ST measurements were followed by a "surface disturbance-relaxation experiment", similar to that reported in [38, 39], which consists in harmonic perturbations induced to the pendant droplet followed by Fourier analysis of the obtained data. The droplet volume was varied with ± 1 mm^3 and the frequencies used were 0.005, 0.008, 0.01, 0.02, 0.04, 0.05, 0.08, 0.1, 0.16 and 0.2 Hz. Figure 14 shows (a) the visco-elastic modulus (|E|) and (b) the phase lag tg(δ) values for the studied solutions. These values were calculated from the E_{Im} and E_{Re} obtained from the Fourier analysis of the rheological data generated by the induced harmonic perturbations.

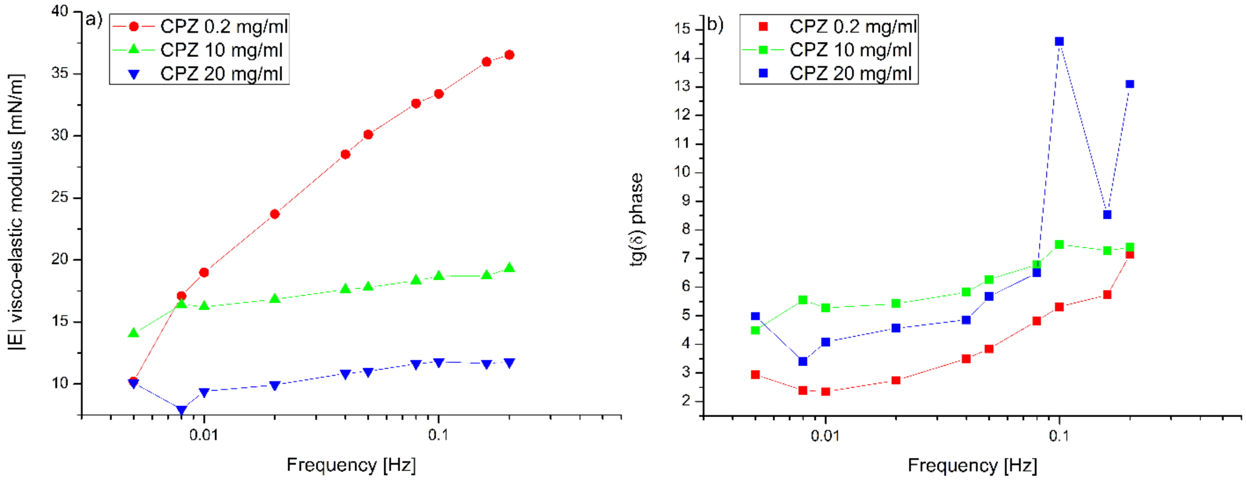


Figure 14. a) Visco-elastic modulus (|E|) and b) phase lag tn(δ) values of CPZ at different concentrations.

It can be observed that by increasing the frequency, both the visco-elastic modulus and tg(δ) increase. The data obtained after the Fourier analysis of the harmonic perturbation measurements are in accordance with the ST results. For the performed measurements, the values of E_{Im} are larger than E_{Re}, which means that the gas/liquid interface of the selected solutions have a predominant elastic character (indicates more "liquid" properties).

CA measurements on UPW, unirradiated and laser irradiated (by Nd:YAG @ 266 nm) droplets generated and detached at 1 g have been carried out on aluminium surface (see Figure 15). Due to droplet impact on surface, damping oscillations in CA data have been observed. One can see that CPZ droplets exhibit lower CA values, thus providing better surface wettability.

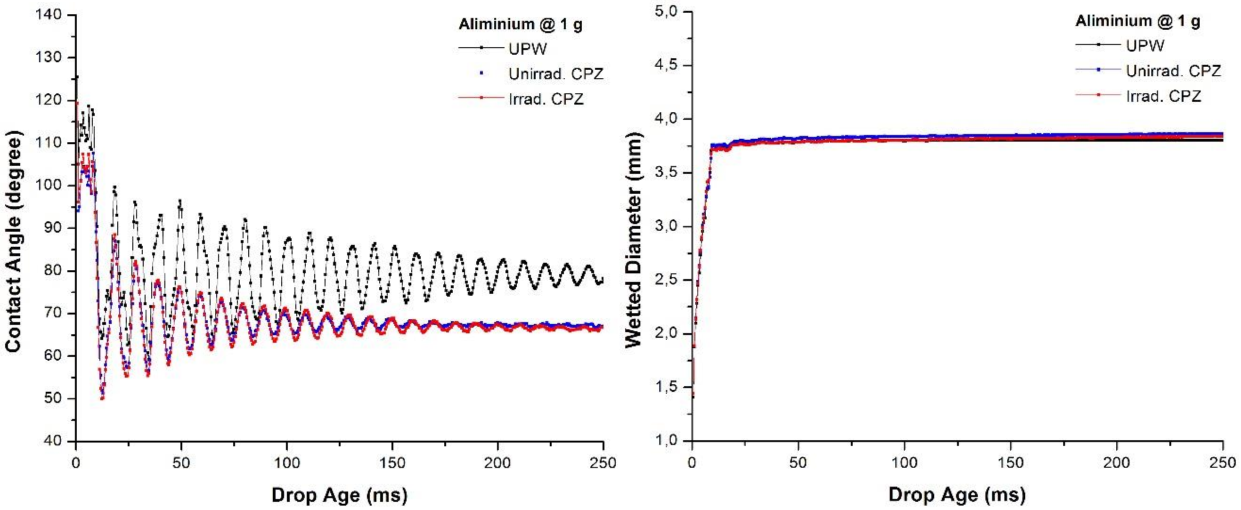


Figure 15. CA and WD evolution of UPW, unexposed and laser exposed CPZ droplets at 20 mg/mL on aluminium surface under terrestrial conditions.

Irradiated CPZ (by Nd:YAG @ 266 nm prior hyper g exposure) has already been studied under hypergravity environment (ESA's Spin Your Thesis! 2015), exhibiting better wetting properties – in the majority of cases – compared to its unirradiated control [40-42].

4.2. Post-analysis

LIF spectra have been recorded both, in 1 g environment prior dropping the capsule and in 10^{-6} g conditions. Figure 16 illustrates the evolution of LIF signal under the above-mentioned g conditions. It can be observed a visible red shift of the fluorescence peak in both g cases, although differences could be emphasized through a kinetic temporal evolution of the fluorescence peak, but also of the spectral bandwidth broadening. The interpretation of the obtained results is currently undergoing.

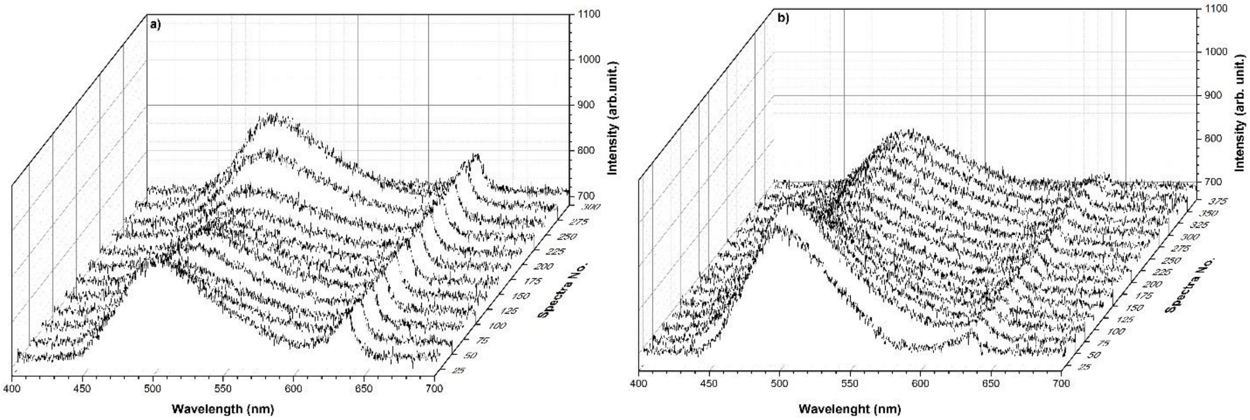


Figure 16. Real time LIF spectra of CPZ at 20 mg/mL irradiated with the 375 nm laser diode a) under terrestrial and b) µg conditions.

Since aluminium represents the basic element in aerospace industry, such surfaces might require decontamination during long-term space missions. That is why the interaction of medicine solutions with such a surface has been studied in µg environment.

The preliminary results corresponded to the predicted ones. It has been expected that in µg the CA values would be higher due to the diminished gravitational force. In Figure 17 it can be observed that in both cases, UPW and irradiated CPZ, the CA values are bigger at 10^{-6} g compared to 1 g conditions. It can be also noticed that the irradiated medicine solution experienced better wetting properties in contrast to the reference UPW droplet.

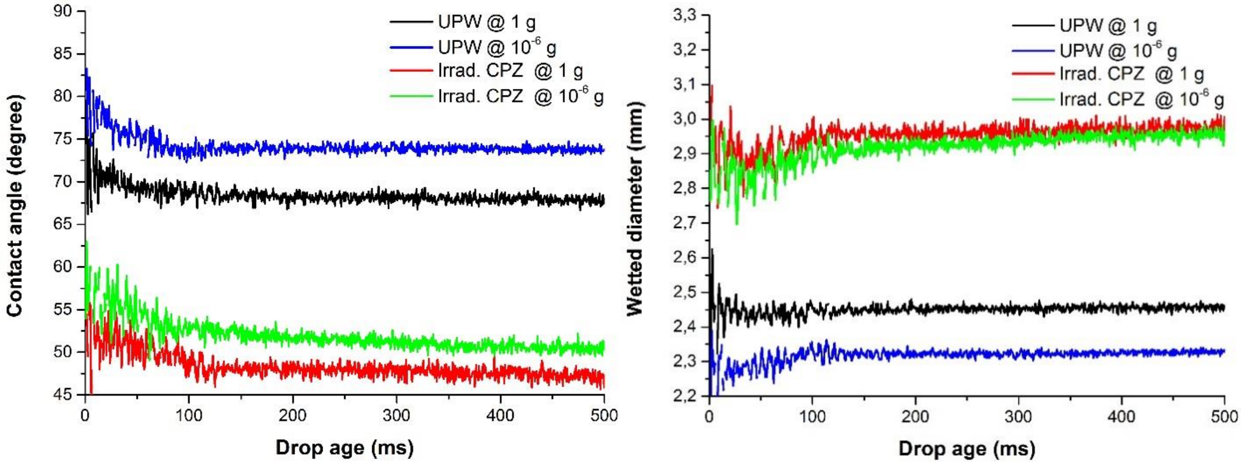


Figure 17. CA and WD evolution of UPW and laser exposed CPZ droplets at 20 mg/mL on aluminium surface under µg conditions.

Regarding WD, one must take into account that in the case of enhanced wetting properties decrease CA corresponds to increased WD, while the opposite situation validates the case of poor wetting characteristics. Figure 17 shows smaller WD values for interactions taking place under µg environment.

It has to be mentioned that data regarding the unirradiated CPZ solution is currently under determination. The Advance software experienced difficulties in determining CA and WD values for such droplets, therefore the DropTES 2018 team seeks for proper solutions to overcome these issues (e.g. improving brightness and contrast of the recorded movies with the PCC 2.6 software of the Miro 3 camera or using other functions to fit droplet contours).

5. Perspectives

Since the obtained results are promising, the DropTES 2018 team intends to finalise the determination and interpretation of data in the upcoming months and publish an article in a peer-reviewed journal.

For the near future, it is also desired to study the laser exposed medicine solutions under simulated µg conditions, by employing the Advanced Engineering Services Uniaxial Clinostat UN-KTM2, received within ZGIP of UNOOSA.

In general, stability of medicines in space may be affected by environmental factors like ionising radiation of cosmic origin, excessive vibrations, variations in temperature and humidity as well as multiple gravity conditions. Regarding the radiation dose, medicines are exposed to values 20 times higher than those experienced on Earth [43]. Since the stability of medicines might be diminished in space, powdered forms of drugs may exhibit prolonged shelf life. Therefore, a solution may consist in taking onboard space shuttles phenothiazines as powders. Afterwards, by preparing drug solutions and subjecting them directly to cosmic radiation, the obtained solutions could be implemented in the treatment of infectious diseases, this fact leading to multifunctional medicines production.

The long-term goal should also consider this fact and would be, also, to test these medicines on the ISS.

6. Impressions

Prof. Pascu: Another successful “experiment” was the fast putting together of a “virtual” research group of young scientists at the beginning of their carriers in multidisciplinary fields such as laser optofluidics and microfluidics. They “functioned” perfectly!

Ágota: The DropTES 2018 project was the most amazing experience and experiment that I ever had. Even if there was a lot of pressure (will our experiment work? or will it survive the impact at the end of the drop?), we had the possibility to work in a fascinating facility with great atmosphere, alongside a dedicated team of drop tower experts. Within that professional and still relaxed environment, we managed to implement our ideas and witnessed our set-up coming to life. I’ll never forget this “adventure”!

Bogdan: Our activity at ZARM, although short, was of great value. We have attained our objective, learned a couple of new things, met new people, and we've done all of that while having fun. My only regret is we didn't stay for a longer period!

Cristian: Taking part in the DropTES program within the multidisciplinary team and collaborating with them in order to obtain the best results in our experiment that was carried out at Bremen Drop Tower in Germany was one of the greatest experiences that I had, both in my professional life and personal life. Firstly, I had the opportunity to work with my teammates, highly skilled professionals in different domains (physics, lasers, biology) and together with them, we’ve successfully set up and finished our set of experiments in microgravity. Secondly, together with my teammates, we had the opportunity not only to see and watch the experiments that are being done at Bremen Drop Tower, but also to have a deep understanding of the engineering technology that resides in the tower and that can be considered its “heart”. Last but not least, we had the opportunity to work with engineers and researchers from abroad, thus opening our perspective regarding fundamental research.

Simona: I’m very grateful for the opportunity to participate in the DropTES programme. For me, this experience was a lesson about how to work in a team and how to eat very fast because the droplets evaporated too quickly. After DropTES, I am sure that this experiment will be a part of my dissertation thesis, where I want to grow some bacteria species to analyse the antimicrobial effect of chlorpromazine.

Acknowledgements

The DropTES 2018 project was supported by UNOOSA, DLR Space Administration and ZARM. The research was also supported by grants of the Romanian National Authority for Scientific Research and Innovation in the frame of CNCS/CCCDI-UEFISCDI, projects PN-III-P2-2.1-PED-2016-0420 and PN-III-P2-2.1-PED-2016-0446 within PNCDI III as well as by the Ministry of Education *via* NUCLEU project PN 1813/2018. The DropTES 2018 team was also sponsored by APEL LASER SRL.

The DropTES 2018 team would like to extend their gratitude for the organisational and logistical support to Ms. Ayami Kojima and Ahmed Osman from SAS of UNOOSA. The team would also like to express their recognition for the scientific and technical assistance to Dr. -Ing. Thorben Könemann, Dipl. -Ing. Fred Oetken and Dipl. -Ing. Jan Siemer from ZARM as well as to LSO of INFLPR, especially to Dr. Dipl.-Ing. Ionuț Relu Andrei, Mr. Marian Cojocaru and Dr. Mihai Boni. The DropTES 2018 team wishes to extend their appreciation to Dr. -Ing. Săndel Simion from the Ultra-Intense Lasers Laboratory (PW) of CETAL, INFLPR, for his help and advices in electrical engineering aspects of the project. Acknowledgements are transmitted to the Photonic Investigations Laboratory (PhIL) of CETAL, INFLPR, particularly to Dr. Emanuel Axente, providing access to the Drop Shape Analyzer device and software for post-analyses.

Last but not least, special thanks are addressed to Mr. Vicențiu Iancu from the Extreme Light Infrastructure - Nuclear Physics (ELI-NP), for his guidance and advices throughout the project.

Abbreviations

µg	microgravity
CA	contact angle
CETAL	Center for Advanced Laser Technologies
CNR-IENI	Consiglio Nazionale delle Ricerche - Instituto per l’Energetica e le Interfasi
CPZ	chlorpromazine
CW	continuous wave
DFT	density functional theory
DLR	German Aerospace Center
DropTES	Drop Tower Experiment Series
EFSM	Engineering Fibrous Smart Materials Group
ELI-NP	Extreme Light Infrastructure - Nuclear Physics
EPR	Experiment Progress Reports
ESA	European Space Agency
ESTEC	European Space Research and Technology Centre
FER	Final Experiment Report
FWHM	full width at half maximum
IEFPCM	Equation Formalism Polarizable Continuum Model
INERA	Multifunctional Nanostructures Project
INFLPR	National Institute for Laser, Plasma and Radiation Physics
ISS	International Space Station
ISSP-BAS	Georgi Nadjakov Institute of Solid State Physics - Bulgarian Academy of Sciences
JIVE	Joint Invention, Visibility and Excellence Project
LIF	laser induced fluorescence
LSO	Laser Spectroscopy Optics Group
PCC	Phantom Camera Control Application
PhIL	Photonic Investigations Laboratory
PW	Ultra-Intense Lasers Laboratory
SAS	Space Applications Section
ST	surface tension
STSM	Short Term Scientific Mission
UB	University of Bucharest
UNOOSA	United Nations Office for Outer Space Affairs
UPB	University Politehnica of Bucharest
UPW	ultrapure water
WD	wetted diameter
ZARM	Center of Applied Space Technology and Microgravity
ZGIP	Zero-Gravity Instrument Project

References

[1] Taylor et al., Toll Mediated Infection Response Is Altered by Gravity and Spaceflight in Drosophila, PLoS ONE 9(1), e86485(1-12), 2014.

[2] Gueguinou et al., Could spaceflight-associated immune system weakening preclude the expansion of human presence beyond orbit?, J. Leukoc. Biol. 86, 1027-1038N, 2009.

[3] Wilson et al., Space flight alters bacterial gene expression and virulence and reveals a role for global regulator Hfq, Proc. Natl. Acad. Sci. USA 104, 16299-16304, 2007.

[4] Nickerson, Effect of Spaceflight on Microbial Gene Expression and Virulence (Microbe), NASA mission, http://www.nasa.gov/mission_pages/station/research/experiments/87.html

[5] Pascu et al., Direct modification of bioactive phenothiazines by exposure to laser radiation, Recent Pat. Antiinfect. Drug Discov. 6(2), 1-13, 2011.

[6] Pascu et al., Exposure of chlorpromazine to 266 nm laser beam generates new species with antibacterial properties: contributions to development of a new process for drug discovery, PLoS ONE 8(2), e55767(1-16), 2013.

[7] Smarandache et al., Optical studies of the spectral properties of phenothiazines. Lett. Drug Des. Discov. 9(4), 352-360, 2012.

[8] Dinache et al., Phenothiazine Derivatives Interaction with Laser Radiation, Rom. Rep. Phys. 65(3), 1078-1091, 2013.

[9] Kristiansen and Amaral, The potential management of resistant infections with non-antibiotics, J. Antimicrob. Chemother. 40, 319-327, 1997.

[10] Kristiansen et al., Non-antibiotic Reverse Resistance of Bacteria to Antibiotics, in vivo 24, 751-754, 2010.

[11] Boni et al., Characterisation of fluorescent pendant droplets; Rom. Rep. Phys., 67(4), 1278-1287, 2015.

[12] Pascu et al., Resonant Interaction of Laser Beams with Pendant Droplets, 184-218, in Laser Optofluidics in Fighting Multiple Drug Resistance, ISBN 978-1-68108-499-2, Ed. M.L. Pascu, Bentham Science Publisher, Sharjah, UAE, 2017.

[13] Pascu et al., Unresonant interaction of laser beams with microdroplets, J. Europ. Opt. Soc. Rap. Public. 7, 12001(1-18), 2012.

[14] Andrei et al., Unresonant Interaction of Laser Beams with Pendant Droplets, 150-183, in Laser Optofluidics in Fighting Multiple Drug Resistance, ISBN 978-1-68108-499-2, Ed. M.L. Pascu, Bentham Science Publisher, Sharjah, UAE, 2017.

[15] Su et al., The development of space microbiology in the future: the value and significance of space microbiology research, Future Microbiol. 8(1), 5-8, 2013.

[16] Crabbé et al., Transcriptional and Proteomic Responses of *Pseudomonas aeruginosa* PAO1 to Spaceflight Conditions Involve Hfq Regulation and Reveal a Role for Oxygen, Appl. Environ. Microbiol. 77(4), 1221-1230, 2011.

[17] Crabbé et al., Spaceflight Enhances Cell Aggregation and Random Budding in *Candida albicans*, PLoS ONE 8(12), e80677(1-24), 2013.

[18] Novikova, Review of the knowledge of microbial contamination of the Russian manned spacecraft, Microb. Ecol. 47(2), 127-32, 2004.

[19] Song and Leff, Identification and characterization of bacterial isolates from the Mir space station, Microbiol. Res. 160, 111-117, 2005.

[20] Taylor, Recovery of medically important microorganisms from Apollo astronauts, Aerosp. Med. 45, 824-828, 1974.

[21] Horneck, Solar UV Radiation, Biological Effects, 85-98, in Encyclopedia of Astrobiology, Ed. M. Gargaud et al., Springer, Berlin, Heidelberg, 2014.

[22] Simon et al., Interaction of solutions containing phenothiazines exposed to laser radiation with materials surfaces, in view of biomedical applications, Int. J. Pharm. 475, 270-281, 2014.

[23] Sudeshna and Parimal, Multiple non-psychiatric effects of phenothiazines: A review, Eur. J. Pharmacol. 648, 6-14, 2010.

[24] Beale and Block, Wilson & Gisvold's textbook of Organic Medicinal and Pharmaceutical Chemistry, Lipicott Williams & Wilkins, 12th Ed., 2010.

[25] Alexandru et al., Biological evaluation of products formed from the irradiation of chlorpromazine with a 266 nm laser beam, Biochem. Pharmacol. 2(1), 1-4, 2013.

[26] Frisch et al., Gaussian Inc., Wallingford CT, 2010.

[27] Lee et al., Quantum Chemistry Simulations of Glycopeptide Antibiotics – Leimkuhler et al., New Algorithms for Macromolecular Simulation, Springer, 343-351, 2006.

[28] Cossi et al., Ab initio study of solvated molecules: A new implementation of the polarizable continuum model, Chem. Phys. Lett. 255, 327-335, 1996.

[29] Improta et al., A state-specific polarizable continuum model time dependent density functional method for excited state calculations in solution, J. Chem. Phys. 125, 1-9, 2006.

[30] Dennington et al., Semichem Inc., Shawnee Mission KS, 2009.

[31] Alexandru et al., Characterization of mixtures of compounds produced in chlorpromazine aqueous solutions by UV laser irradiation: their applications in antimicrobial assays, JBO 20(5), 051002, 2015.

[32] Andrei et al., Chlorpromazine transformation by exposure to ultraviolet laser beams in droplet and bulk, Eur. J. Pharm. Sci. 81, 27-35, 2016.

[33] Drop Tower Operation and Service Company, ZARM FABmbH, ZARM Drop Tower Bremen User Manual, 2012.

[34] United Nations Office for Outer Space Affairs, United Nations Programme on space Applications, Teacher's Guide to Plant Experiments in Microgravity, Human Space Technology Initiative, United Nations, New York, 2013.

[35] Drop Tower Operation and Service Company, ZARM FABmbH, Weightless in the Drop Tower Bremen, 2015.

[36] Kabov and Zaitsev, The Effect of Wetting Hysteresis on Drop Spreading under Gravity, Dokl. Phys. 58(7), 292-295, 2013.

[37] Brutin et al., Evaporation of Ethanol Drops on Heated Substrate Under Microgravity Conditions, Microgravity Sci. Technol. 22, 387-395, 2010.

[38] Nastasa et al., Properties of polidocanol foam in view of its use in sclerotherapy, Int. J. Pharm. 478, 588-596, 2015.

[39] Staicu et al., Photophysics of covalent functionalized single walled carbon nanotubes with a porphyrin-type photosensitizer, Rom. Rep. Phys. 67(4), 1457-1466, 2015.

[40] Simon et al., Interaction of Laser Exposed Non-Antibiotic Solutions with Target Surfaces in Hypergravity Conditions: ESA "Spin Your Thesis!" Campaign, Proc. F552, "1st Symposium on Space Educational Activities", Padova, Italy, 9-12 December 2015.

[41] Simon et al., Microvolumetric Droplets in Air in Hypergravity Conditions, 428-445, in Laser Optofluidics in Fighting Multiple Drug Resistance, ISBN 978-1-68108-499-2, Ed. M.L. Pascu, Bentham Science Publisher, Sharjah, UAE, 2017.

[42] Simon et al., Impact dynamics of laser modified medicine droplets on target surfaces under hypergravity conditions, Hypergravity Workshop, Noordwijk, The Netherlands, 25-26 January 2018.

[43] Haynes, Space motion sickness and alien microbes: learning from astronauts, Pharm. J., 2013.