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MICRO-PIV ANALYSIS OF PARTICLE SIZE AND CONCENTRATION EFFECTS IN MICROSYSTEMS WITH PHARMACEUTICAL APPLICATIONS

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Abstract

A state-of-the-art Micro-Particle Image Velocimetry (μPIV) system was assembled at the Bundeswehr University Munich to evaluate the flow inside microsystems, designed and fabricated by the Mikropart group, for pharmaceutical and biological applications (http://www.mikropart.de). An analysis of seeding-particle-size effect was performed on the flow inside an L-shaped micro-channel and variations of the velocity profiles were observed for the larger particle sizes tested. Furthermore, the flow in the microchannel was loaded with increasing concentrations of titanium dioxide (TiO_2) to test for multiphase effects induced by third-party components used for future applications of the microsystems. The inspection of the loaded flow suggests that the concentrations of TiO_2, evaluated in this study, do not have a strong effect of the channel flow.

Introduction

Over the last decades, the biological and pharmaceutical fields have seen substantial advances in the development of micro-electromechanical system (MEMS) technologies. Research on microfluidic devices began more than 25 years ago and its applications now range from flow sensors used for measurement of minute liquid flows (Gravesen et al. 1993), to biochips capable of characterizing and quantifying biomolecules (Vo-Dihn & Cullum 2000). Currently, the Mikropart group is developing innovative micro-structures with several applications in the biological and pharmaceutical fields. The Mikropart group is a research collaboration between several research institutes at the TU Braunschweig and the Bundeswehr Universtiy Munich including:

- Institute of microtechnology
- Institute of particle technology
- Institute of biochemical engineering
- Institute of surface technology
- Institute of pharmaceutical technology
- Institute of fluid mechanics and aerodynamics

Among the novel designs being developed are micro-bioreactors used as screening tools for microbial processes. Micro-bioreactors have demonstrated the advantages of rapid heat and mass transfer due to their small scale and improved surface-area-to-volume ratio (Demming et al. 2008). Other designs include micro-channel geometries intended to cause an effect on the dispersion of nano-particles. An increased interest in nano-particles across many industries has taken place due to the enhanced efficiency that micro-chips provide in the biological sciences. Pharmaceutical agents are dependent on dispersed nano-particles in fluids. However, it is a challenge to design structures to handle such small particles due to the strong inner-forces that occur when they are mixed, which promote the formation of aggregates and agglomerates (Lesche et al. 2008). One of the several industrial applications of dispersed nano-particles includes the use of modified solid lipid nanoparticles, also called nanostructured lipid carriers, as delivery systems for organic and inorganic sunscreens. Furthermore, they have demonstrated an improvement of the protection factor by adding TiO_2 in aqueous media without the use of complex formulations (Villalobos & Müller 2006). Along with the various ideas and designs being developed by the Mikropart group, computational fluid dynamic simulations are being performed to enhance the performance of the micro-chips, in their respective applications. On the other hand, to validate the simulations and really enhance the micro-structures and their performance, a reliable experimental flow diagnostic technique is required. This technique must meet the spatial resolution necessary to resolve and analyze the natural phenomena that occur in the micro-flows that run through the systems. Particle Image Velocimetry (PIV) is a non-intrusive flow diagnostic technique that meets the high demands of this particular research. It has been used efficiently and reliably to evaluate macroscopic flows for several decades. Furthermore, in the last ten years, it has been further developed to successfully measure velocity fields in multiple micro-geometries with a myriad of applications in science and engineering (Santiago et al. 1998; Hsieh et al. 2004). The primary objective of this research is to develop a top-of-the line experimental facility to perform high-quality μPIV measurements on the previously mentioned micro-structures to validate the numerical simulations of the flow inside them. However, in order to achieve this task, the experimental parameters that affect the flows in question must be evaluated and thoroughly understood. Besides the general experimental setup and procedure, the data evaluation process and analysis of the flow inside an L-shaped micro-channel is reported. The flow in the channel was seeded with particles varying in size, to test for tracer-particle- size effects on the flow. Furthermore, TiO_2 was added to the flow in increasing concentrations to evaluate the effect of third-party loading on the flow behavior as well as on the quality of the images and results, due to the added opacity of the fluid induced by the increasing concentration of TiO_2 solution.

Experimental Setup

Polystyrene latex particles, fabricated by Microparticles GmbH, were used to seed and track the flow. All of the seeding particles used were coated with fluorescent Rhodamine B. Four particle sizes were used with mean diameters, $d_{p,}$ of 0.515 μm, 1.02 μm, 4.93 μm, and 10.17 μm respectively. The particles originally come dissolved in water at a concentration of 25mg/ml. All experiments were made with a concentration of 2.5% particle-solution volume, dissolved in isopropanol, and continuously stirred with an ultrasonic homogenizer (model 300 by Biologics Inc.). The flow was generated by withdrawing the homogeneous seeded solution through the channel using a precision Nexus 3000 syringe pump, manufactured by Chemix. A μPIV system was used to acquire the particle images. The system consists of an Axio observer Z1 inverted microscope manufactured by Carl Zeiss, a two cavity frequency-doubled

Litron Nano L Nd:Yag laser system, and a 12-bit, 1280 × 1024 pixel², interline transfer CCD camera (PCO Sensicam). A schematic of the μPIV system is shown in Figure 1.

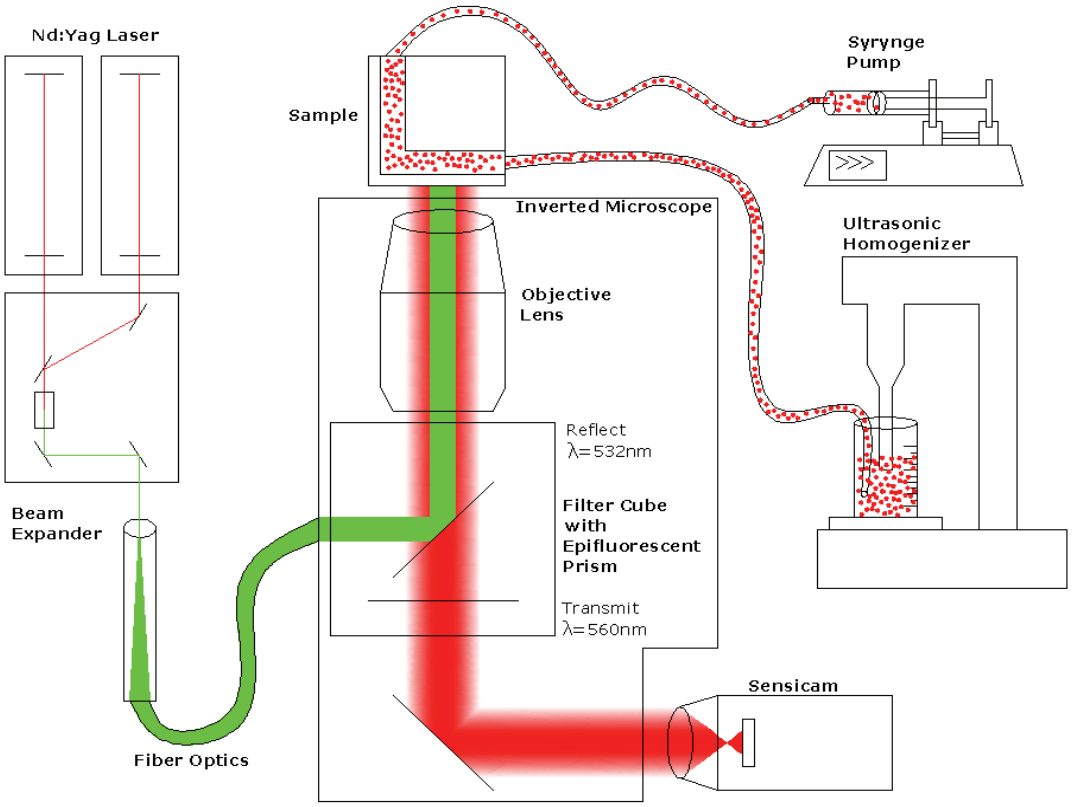

Figure 1. Schematic of μPIV system

The system is installed on an optical table to damp vibrations. The laser beam is expanded after leaving the laser cavity and delivered to the back aperture of the microscope via fiber optics. The microscope is equipped with an epi-fluorescent filter cube and an objective lens which relays the laser light on to the sample. The filter cube consists of an exciter (green filter), an emitter (red filter), and a dichroic mirror. The light entering the back aperture of the microscope passes through the exciter and is reflected because the dichroic mirror only transmits wavelengths longer than 585 nm. The filter cube conducts the light beam into the objective lens which focuses it on the sample, illuminating the seeded flow volume. The tracer particles' fluorescent coating absorbs the green laser light (532 nm), and emit a distribution of longer wavelength, red light (610 nm). The light scattered by the tracer particles is imaged and passes through the emitter in the filter cube, where green light, scattered from artifacts other than the seeded particles (backreflections), is blocked leaving only the fluorescent light recorded on the CCD sensor of the camera. Recordings were made using the DaVis 7.2 software package from LaVision. Images were acquired in double exposure mode, where the camera shutter is activated two times, separated by a predetermined time delay Δt.

The TiO_2 suspensions were fabricated at the Institute of Pharmaceutical Technology at TU Braunschweig. They originally come dissolved in double-distilled filtered water, mixed with polysorbate 80 and simethicone antifoamer, with a concentration of 2% alumina-stearic acid coated titanium dioxide, which is 100% rutile crystal structure and has a particle size of approximately 17 nm. For further details on the fabrication and components, the reader can refer to Villalobos & Müller 2006.

The micro-channels are fabricated out of elastomeric polydimethylsiloxane (PDMS) on a 1 mm thick glass plate. For details on the procedure and fabrication, the reader can refer to Lesche et al. 2008.

Results

Particle size study

Measurements at six sections of a rectangular 960 × 140 μm² L-shaped micro-channel were performed and results will refer to them by their respective location number according to Figure 2.

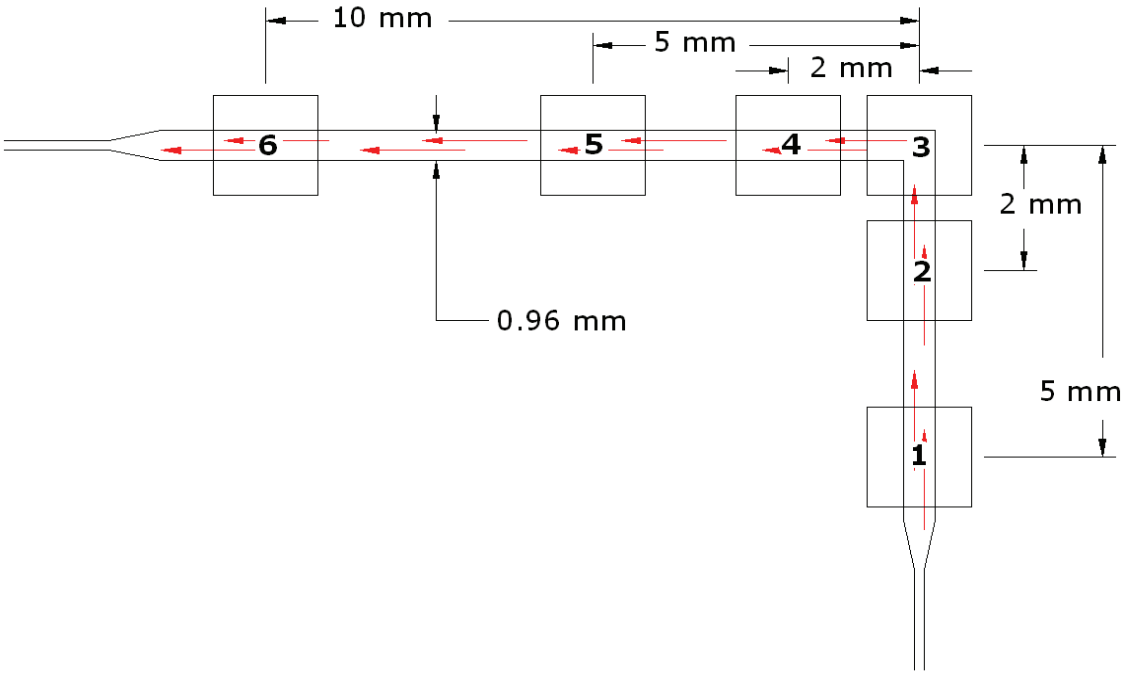

Figure 2. Schematic of L-shaped micro-channel

All recordings were made with a Zeiss EC-Neofluar objective lens with a magnification of 10×. The numerical aperture of the lens was 0.3, thus yielding a depth of focus of approximately 7 μm. Isopropanol flow, seeded with tracer particles of mean diameters, $d_{p,}$ of 0.515 μm, 1.02 μm, 4.93 μm, and 10.17 μm was analyzed. Raw images of flows seeded with different particle sizes are displayed in Figure 3. The flow was withdrawn from the continuously stirred reservoir at 100 ml/hr. Isopropanol was used to avoid the regular occurrence of air bubbles present in water; bubbles stick to corners, alter the flow, and modify or disguise the

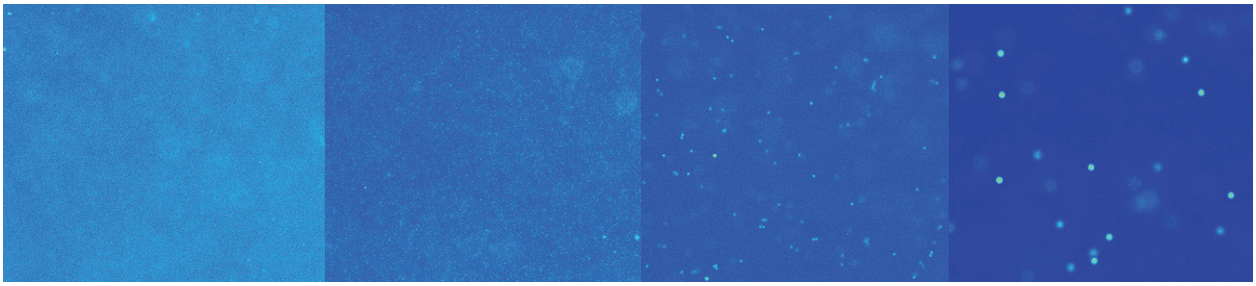

Figure 3. Isopropanol flow seeded with d_p = 0.515 μm, 1.02 μm, 4.93 μm, 10.17 μm (left to right)

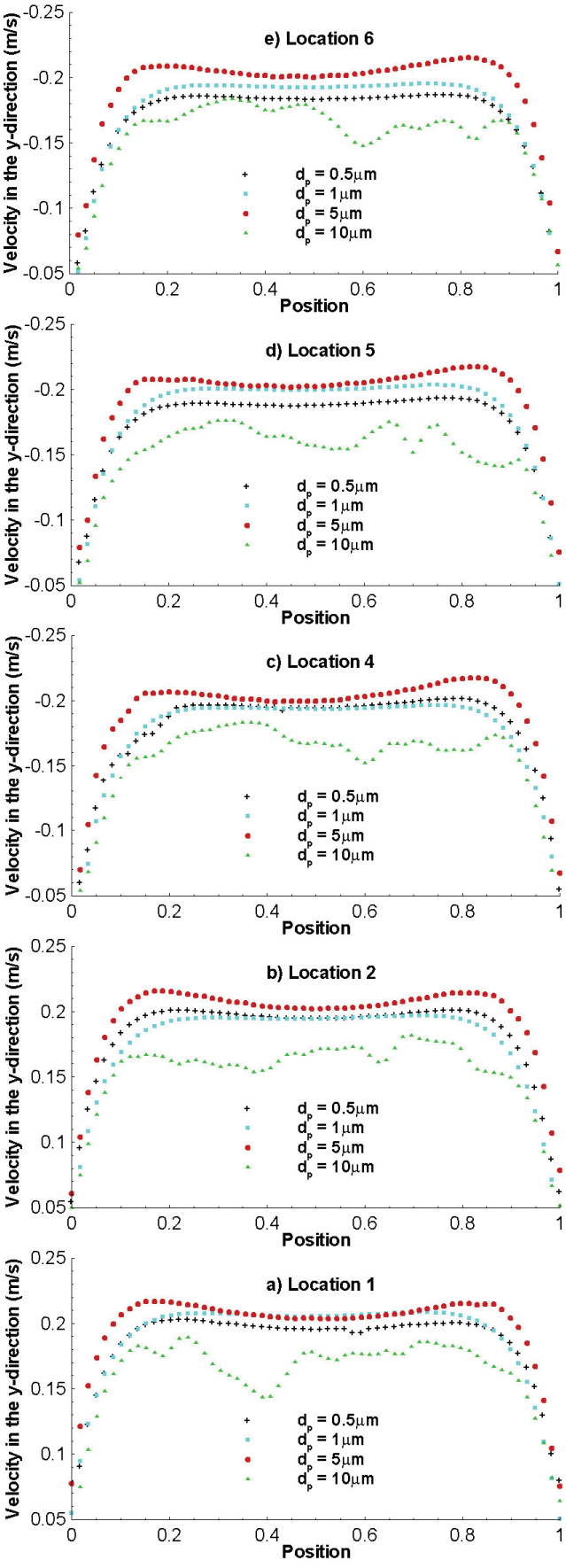

Figure 4. Velocity profiles for increasing tracer particle sizes at different straight locations in the L-shaped micro-channel.

very effects that the experiment is designed to detect. The focal plane of the optical system was located at the center of the channel. This location was determined by focusing the system on the top and bottom walls, recording their locations, and moving the focused image to the mid-point between the walls. All recordings consisted of 200 double exposures. Basic image processing was performed on the recordings by taking the average light intensity recorded by each pixel throughout the series, and subtracting it from the value recorded by the same pixel in each recording. This procedure eliminates the bright spots generated by particle clusters stuck to walls and other back-reflections that do not move with the flow. Velocity vectors are then calculated using the cross correlation methods of conventional PIV. PIV analysis was carried out with the DaVis 7.2 software package from LaVision. As opposed to conventional PIV, considering the small tracer particle sizes and slow flow velocities, Brownian motion can become a substantial source of error in μPIV measurements. However, due to the fact that Brownian motion is a zero mean random process, its influence can be considerably reduced by adding the correlation planes to obtain mean velocity vectors.

For the purposes of this analysis, all recordings consisted of 200 double exposures. Furthermore, since the flow was laminar and stationary, an ensemble cross-correlation approach was used to calculate the mean velocity vector fields. A normalized multi-pass algorithm with decreasing interrogation window sizes of 64 × 64 pixel² and 32 × 32 pixel² was used with 50% overlapping of the interrogation windows.

Flow seeded with increasing particle sizes was evaluated in the L-shaped micro-channel. Figure 4 shows the velocity profiles in the straight sections of the channel: 1, 2, 4, 5 and 6. Each plot displays four velocity profiles, corresponding to different tracer particle sizes. Tracer particles with mean diameters, $d_{p,}$ of 0.515 μm, 1.02 μm,

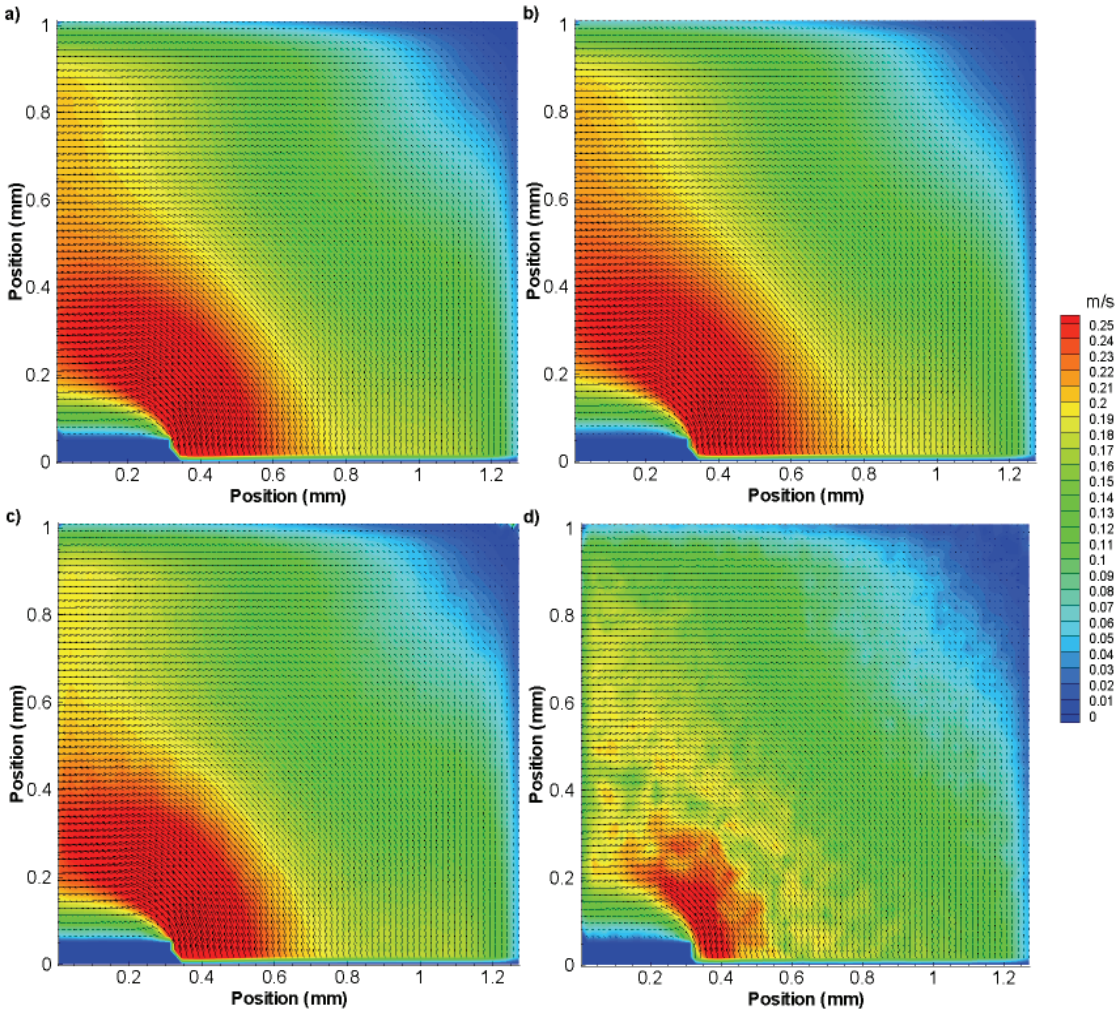

Figure 5. Velocity fields at location 3 for different tracer particle sizes: a) d_p=0.515 µm, b) d_p=1.02 µm, c) d_p=4.93 µm, d) d_p=10.17 µm.

4.93 µm, and 10.17 µm were tested to evaluate the effect of particle size on the flow. Note that the flow in the channel does not develop into a parabolic profile. However, the flow seeded with smaller particles, d_p=0.515 µm and d_p=1.02 µm, displays a consistent pattern throughout the channel of higher flow velocity away from the walls. On the other hand, the flow seeded with 4.93 µm particles, shows a slight decrease in velocity towards the center of the channel. It is possible that due to the increased size of the particles, the flow becomes inhomogeneous enough that multi-phase effects are introduced. Moreover, the flow seeded with 10.17 µm particles, displays a non-uniform velocity profile throughout the channel. It is likely that the interaction between large particles moving in a small fluid volume is strong enough to make the solution heterogeneous where agglomerates occur slowing down the flow in certain areas. It seems clear that at this particle diameter, the flow is strongly affected and a multiphase flow is introduced. To make sure that the lack of uniformity present in these velocity profiles was not a product of the data processing applied, another processing approach was used to confirm the physicality of the results. The 200 image pairs were cross-correlated individually with larger interrogation windows. The mean velocity vectors where then averaged and a velocity profile was obtained. Although the resolution of these profiles was lower than the ones presented in Figure 4, both approaches resulted in similar non-uniform velocity profiles. Additionally, the velocity vector fields in location 3 of the L-shaped micro-channel, for the four particle sizes tested, are shown in Figure 5. The non-uniform na-

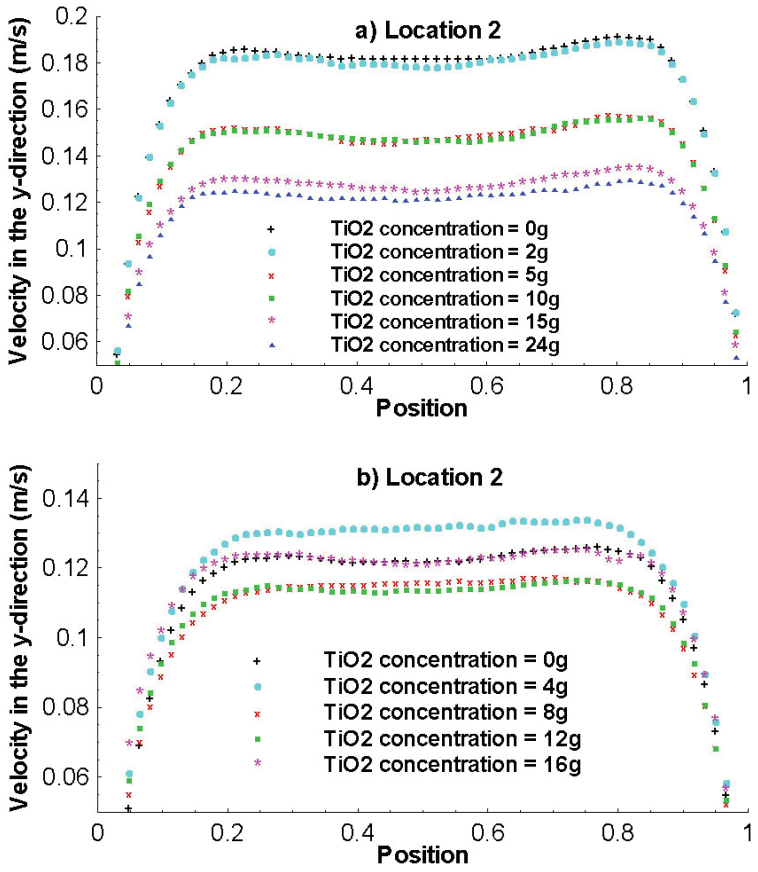

Figure 6. Velocity profiles for different concentrations of TiO_2 suspension solution at location 2 in the L-shaped channel.

ture of the flow seeded with 10.17 µm particles is also evident in Figure 5d. It is clear from this plot that the flow is disturbed by the large particle size and symptoms of multi-phase flow become evident.

TiO_2 concentration study

Next, isopropanol flow seeded with 2.5% particle solution of mean diameter d_p=4.93 µm, was loaded with increasing concentrations of TiO_2 suspension solution and evaluated inside the micro-channel. All measurements of flow loaded with TiO_2 were performed in location 2 of the channel (see Figure 2). First, seeded isopropanol without TiO_2 was evaluated. Then, TiO_2 suspension solution was gradually added and tested. Note that although the seeded flow became considerably more opaque with increasing concentrations of the milky TiO_2 suspension, the light scattered by TiO_2 particles was efficiently blocked by the epi-fluorescent filter cube. There was no substantial difference in the particle images with low and high TiO_2 concentration. Figure 6a shows velocity profiles for increasing amounts of TiO_2 suspension solution added to the flow. This figure suggests that the increasing concentration of TiO_2 causes the flow to slow down but the velocity difference between concentrations does not follow a sensible pattern. For this reason, the experiment was performed a second time and the channel was thoroughly cleaned after each concentration was evaluated. Figure 6b also shows velocity profiles for increasing concentrations of TiO_2. As can be seen in this plot, the profile for the lowest concentration is very similar to the profile with the highest concentration. This suggests that there is no clear effect introduced by the loading of the flow with TiO_2 suspension solution. More highly concentrated suspensions will be tested in the future. As for the velocity variation present in the profiles in Figure 6, it may be caused by accumulation of agglomerates of TiO_2 in the inlet of the micro-channel as loaded flow runs continuously through it. This would explain the orderly decrease in velocity that can be seen in Figure 6a.

Conclusions and Outlook

A state-of-the-art µPIV system was successfully assembled and tested at the Bundeswehr University Munich to make high-resolution velocity measurements inside microstructures, designed and fabricated by the Mikropart group in TU Braunschweig. A study of basic experimental parameters was performed on the flow inside a rectangular L-shaped micro-channel. Isopropanol flow seeded with tracer particles of mean diameters, $d_{p,}$= 0.515 µm, 1.02 µm, 4.93 µm, and 10.17 µm was evaluated in several sections of the channel. The seeding of

4.93 µm tracer particles displays slight differences in the velocity profiles of the flow at all sections of the channel, showing a slight decrease in the flow velocity towards the center. Moreover, a confirmation that particle size does have an effect was obtained by seeding the flow with 10.17 µm particles. The velocity profiles for the flow seeded with these particles were not uniform in any of the sections evaluated, and displayed clear differences from the flows seeded with smaller particles. It is likely that the interaction between large particles moving in a small fluid volume is so strong that the solution becomes heterogeneous and multi-phase effects are introduced. An improvement of the measurement technique, which would contribute to the characterizing and understanding of this effect, would be the use of time resolved µPIV on the flow in the channel.
Lastly, isopropanol flow, seeded with 4.93 µm particles was loaded with increasing concentrations of TiO_2 .The presence of this third party component did not seem to have an effect either on the image quality or in the flow characteristics at the tested concentration levels. On the other hand, a blockage on the inlet of the channel was detected after circulating loaded flow for some time. Agglomerations of particles and the suspension solution seem to accumulate at the inlet and decrease the flow rate in the channel. Therefore, careful consideration of differences in the mean velocities should be taken, as debris accumulation at the ends of the channel could be playing a significant role. Higher concentrations of TiO_2 and other organic nano-particles will be tested in the future for a more thorough analysis of loaded flows inside micro-channels.

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