TOWARDS SELECTORFREE SEPARATION OF CHIRAL MOLECULES: ENANTIOSELECTIVE SEPARATION OF MICROPARTICLES IN A MICROFLUIDIC DEVICE

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ABSTRACT

We developed two model experiments for a continuous separation strategy for chiral molecules without the need for any chemical selection- or derivatization agents. By breaking all relevant spatial symmetries with either a structured sidewall or a tilted array of posts in a microfluidic channel, chiral microparticles are forced to migrate into different directions. In our experiments, separation efficiencies of 85% and up to 100%, respectively, could be demonstrated by introducing asymmetric flow environments in microchip systems.

KEYWORDS: Enantiomers, Chirality, Enantioselective separation , Microarray

INTRODUCTION

About one half of the drugs on the market are chiral and only 25% of all drugs are administered as pure enantiomers [1]. Because living organisms are highly chiral environments, their reaction to different chiral forms of a molecule can be completely different. Consequently, the molecules have mostly different pharmacological activities underlining the need for preparational and analytical techniques. Traditionally, chiral selectors are used that specifically bind only one form in a chromatography setup. This approach, however, requires the identification of new selectors for every new analyte and is working in batch-mode only. In contrast to these standard techniques, we experimentally realized and explored an alternative selector-free and continuously working separation concept with model microparticles [2] based only on physical mechanisms and a theoretical evaluation [3,4].

EXPERIMENTAL

According to Curie's dissymmetry principle [5] the symmetry elements of a physical cause have to be reencountered in the outcome. Therefore, we designed and fabricated two practically different microfluidic devices with broken axial symmetry (see Fig. 1). Because of these broken symmetries, chiral microparticles will be deflected axially within the flow. Principle A involves structured sidewalls, generating a deformed Hagen-Poiseuille-flow (Fig 1a,b). Any asymmetric object, like a chiral microparticle will then migrate differently in contrast to its mirror image within this flow profile.

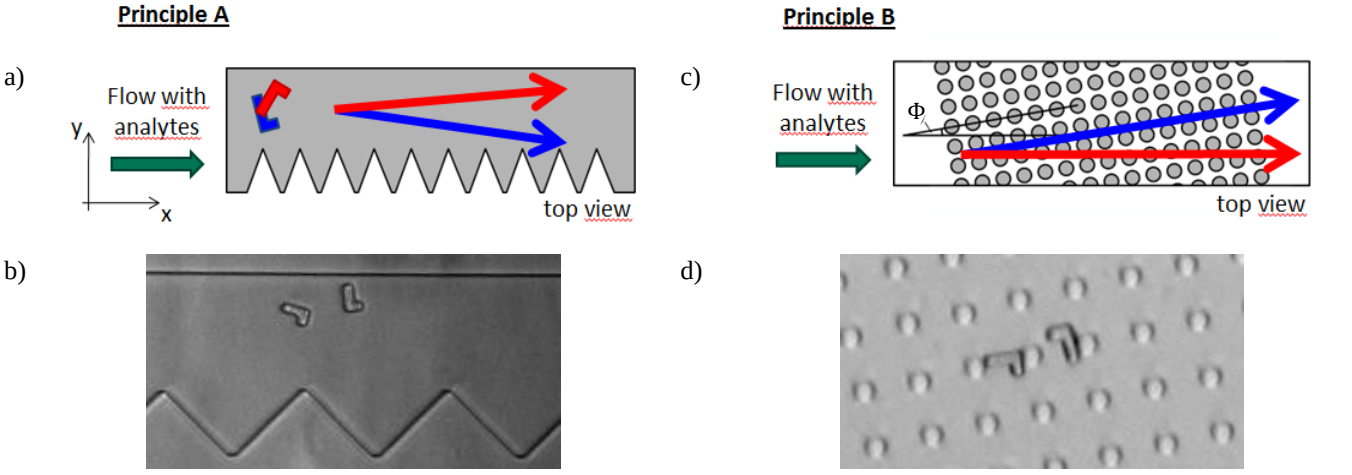

Fig. 1: a) Device A involves a structuring of one of the sidewalls. Injected chiral microparticles will be separated due to the asymmetric flow profile. b) Micrograph of device A with microparticles. Particle size: 15µm x 9µm, channel width: 40-60 µm, period length: 50 µm, height: 6 µm. c) Device B is based on a an array of structured posts, where the main axis is tilted against the x-axis by a certain angle Φ. d) Micrograph of device B. Channel width: 1000 µm, channel height: 6 µm, periodicity of the post array: 20 µm, post diameter: 6,8 µm.

The idea of the second principle B is the exploitation of an array of microstructured cylindrical posts in the channel (Fig. 1c,d). This post array is tilted by a predefined angle Φ with respect to the x-axis and the asymmetry is therefore introduced by the different interaction of the particles with the posts. In both experiments, the particles are driven pneumatically by applying an external air pressure difference to the reservoirs at the end of the channel. The resulting migration speed of the particles is in the order of 50-100 µm/s.

The microfluidic chips were fabricated with a simple and straightforward soft lithography procedure. The L and Γ shaped microparticles with dimensions of 15x9 µm were fabricated as reported in [2], where a large quantity of particles are structured with SU-8 onto a small piece of a silicon wafer without any sacrificial layer. After an optical inspection, the wafer piece is placed in a small vial containing water and a surfactant solution. The particles are then removed from the surface by placing the vial in an ultrasonic bath for 10-30 seconds. To keep their chirality, the height of the particles (3 µm) is chosen in such a way, that they fit into the 6 µm high channels but cannot rotate along their long axis. This effectively reduces the experimental geometry to two dimensions in this model system, making further measures to break the symmetry in the third dimension obsolete.

RESULTS AND DISCUSSION

Fig. 2a shows the experimental trajectories using the microflow channel with one structured sidewall (principle A). Due to their interaction with the asymmetrically designed flow profile in this channel (Fig. 2b) the particle species split up according to their chirality. It could be demonstrated that one species approaches the flat wall whereas the other one accumulates in the vicinity of the structured wall. 85 % of all injected particles were recognized by the system and were correctly sorted after a maximum traveled distance of 1800 µm. The other 15 % did not show any (correct or false) action.

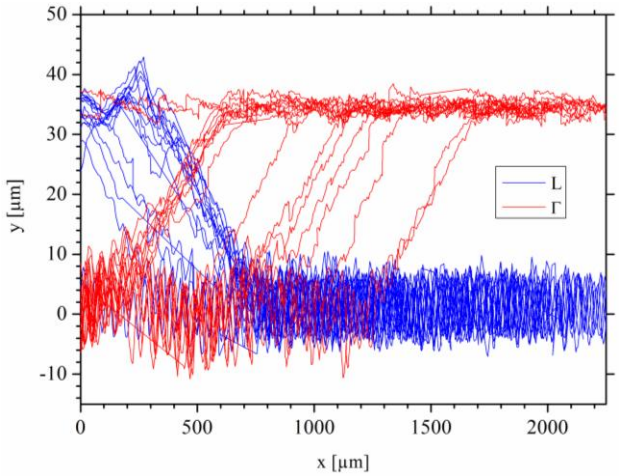

Fig. 2a: Experimental separation results obtained within a channel with a structured sidewall (principle A). In 85% of all realizations, the chiral microparticles have been recognized (shown here). The rest (15 %) did not show any (correct or false) action.

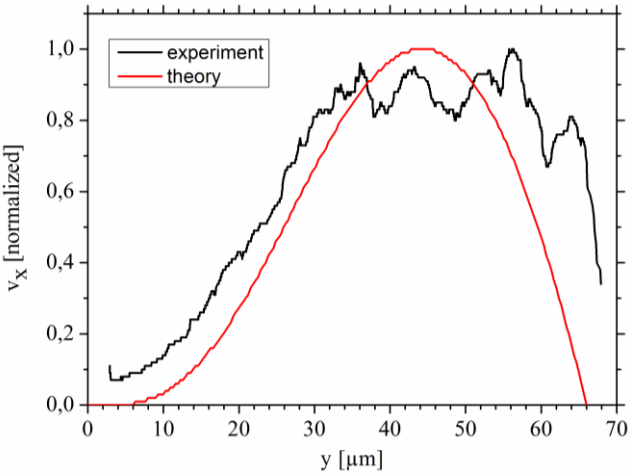

Fig. 2b: Experimental and theoretical flow profiles within the micro channel with structured sidewalls. The typical Hagen-Poiseuille-flow profile is shifted away from the structured wall which induces the asymmetry in the system. Typical flow speeds are in the order of 100µm/s.

For the second setup (principle B), which does not rely on shear flows, the results are shown in Fig. 3a,b. Here, all of the injected particles were recognized and sorted correctly after only a few elementary cells with a predefined array tilting angle of $\Phi = 15°$. Typical migration speeds are in the order of 50-100 µm/s. A significant angle of separation of $\Delta\theta_{15°} = 22.76° \pm 3{,}53°$ could be demonstrated.

We found in accordance with theoretical simulations that the system reacts very sensitive to minor changes of the array tilting angle Φ (Fig. 3b). For $\Phi = 12°$ the angle of separation changes sign and becomes more insignificant $\Delta\theta_{12°} = -5.8° \pm 6.0°$. This indicates, that there are certain windows for efficient separation depending on the actual value of Φ.

CONCLUSIONS

Two model experiments to separate L and Γ shaped chiral microparticles are presented. Both designs rely on breaking the spatial symmetry of the particles' environment. A first concept were the hydrodynamic flow profile is modified to be asymmetric exhibited 85% efficiency and no explicit false results. In a second concept, a tilted array of cylindrical posts inside the channel lead to even 100% efficiency.

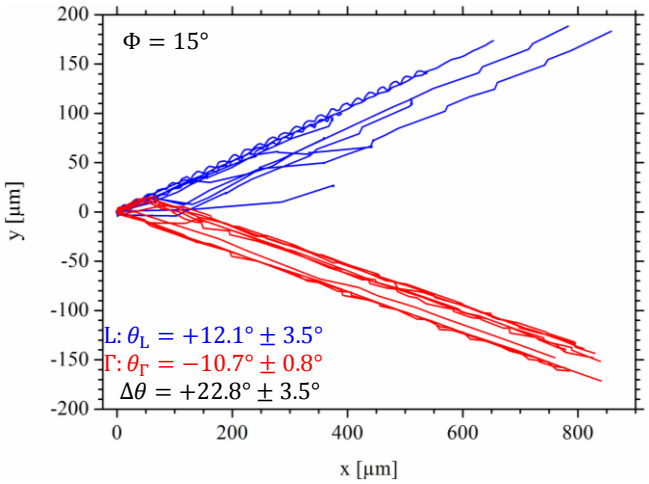

Fig. 3a: Separation results obtained with a structured post array (principle B) for a tilting angle of $\Phi = 15°$. *The single particle trajectories show effective separation angles between both mean trajectories of* $\Delta\theta_{15°} = 22{,}8° \pm 3{,}5°$ *with 100% efficiency in all realizations.*

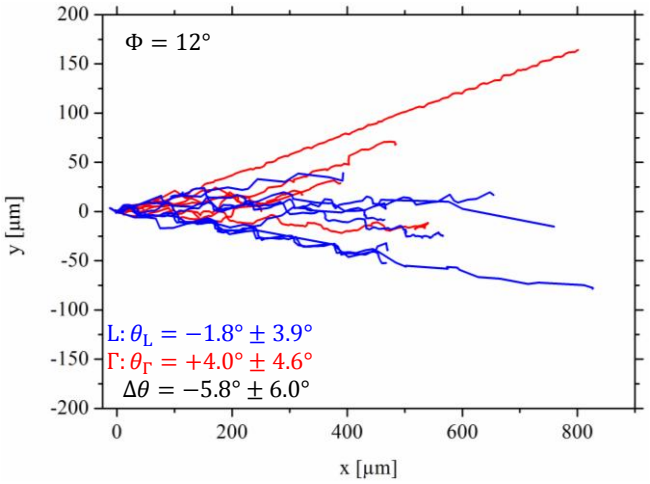

Fig. 3b: Separation results obtain with a structured post array for a tilting angle of $\Phi = 12°$. *The resulting angle of separation is now only* $\Delta\theta_{12°} = -5.8° \pm 6.0°$. *The results indicate, that there are certain windows of separation which depend strongly on* Φ.

This is the first attempt to realize enantioselective separation with model systems at the micrometer scale. The selector-free microfluidic approach offers good opportunities for parallelization and continuous, maintenance-free operation. In the future, emphasis is put on enantioselective separation of objects on the molecular scale - like proteins - with concepts of further miniaturization (e. g. self assembly). Such a cheap and straightforward device might have considerable industrial impact, as more pharmacological agents can be purified more easily, which might make them better tolerable and thus simplify the accreditation process.

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REFERENCES

[1] G. Gübitz and M. G. Schmid, "Chiral Separation by Chromatographic and Electromigration Techniques. A Review", Biopharm. Drug Dispos., vol. 22**,** pp. 291, 2001.

[2] L. Bogunovic, D. Anselmetti and J. Regtmeier, "Photolithographic fabrication of arbitrarily shaped SU-8 microparticles without sacrificial release layers", J. Micromech. Microeng**.**, vol. 21, pp 027003, 2011

[3] D. Speer, R. Eichhorn, P. Reimann, "Exploiting lattice potentials for sorting chiral particles", *Phys. Rev. Lett.*, vol. 105, pp. 090602, 2010

[4] R. Eichhorn, "Enantioseparation in microfluidic channels", Chem. Phys., vol. 375, pp. 568, 2010

[5] P. Curie, "Sur la symétrie dans les phénomènes physiques", J. Phys., vol. 3, pp. 401, 1894

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