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The use of a linear Halbach array combined with a step-SPLITT channel for continuous sorting of magnetic species

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Abstract

The Quadrupole Magnetic Sorter (QMS), employing an annular flow channel concentric with the aperture of a quadrupole magnet, is well established for cell and particle separations. Here we propose a magnetic particle separator comprising a linear array of cylindrical magnets, analogous to the array proposed by Klaus Halbach, mated to a substantially improved form of parallel-plate SPLITT channel, known as the step-SPLITT channel. While the magnetic force and throughput are generally lower than for the QMS, the new separator has advantages in ease of fabrication and the ability to vary the magnetic force to suit the separands. Preliminary experiments yield results consistent with prediction and show promise regarding future separations of cells of biomedical interest.

Keywords

Magnetic separation; Particle fractionation; SPLITT; step-SPLITT

1. Introduction

The continuous sorting of magnetized species is ubiquitous for biomedical applications. Sorting by means of immunomagnetic methods is widely used for stem cell enrichment and cancer cell isolation and identification. Several devices are currently employed, but techniques using open channels, without membranes or filters, are still rare. One of them is the Quadrupole Magnetic Sorter (QMS) [1] developed for high throughput separations of magnetized biological cells [2]. The QMS has an axial symmetry and utilizes a quadrupole magnet that generates an axisymmetric magnetic field in the thin annulus between the two concentric cylinders defining the annular SPLITT-flow Thin (SPLITT) channel separator [1]. The annular channel is compatible with the characteristic solenoidal (source-less) magnetic field. On the other hand, the conventional parallel plate SPLITT channel [3,4] has not been adequately developed for magnetic separations because of the difficulty of generating uniform magnetic fields and high gradients between parallel planes. A parallel plate magnetic SPLITT configuration has been proposed [5], but limitations due to mating the

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channel geometry to a solenoidal magnetic field predict inadequacy for high throughput separations.

We present two innovations: 1) the use of a linear Halbach array [6] for generating a very uniform magnetic field and gradient, and 2) the use of a splitterless SPLITT channel, or step-SPLITT channel, [7] having walls thinner than those of conventional channels. Their combination results in the magnetic step-SPLITT device (Mg-s-SPLITT), that is well adapted to high throughput separations and to microfluidic sorting.

2. Magnetic field

A linear Halbach array has been proposed as a magnetic bandage in application to targeted magnetic drug delivery [8,9]. The array is used to obtain a uni-directional particle magnetophoresis. The array consists of an arrangement of magnets, each having uniform polarity thorough their volumes. The direction of polarity is varied by precise angles between successive magnet units so that the magnetic field lines are reinforced on one side of the array, while they are almost cancelled on the opposite side. We adopted a linear array of diametrically polarized cylinders for the construction as shown in Fig. 1. It is demonstrated that such a linear configuration of magnets can be used for continuous particle separation. Our linear Halbach array comprises two rows of permanent magnet cylinders of 16 units each, supported by aluminum frames. The cylinders are nickel-plated neodymium-iron-boron (NeFeB) (42 MGOe energy product) and 2.54×2.54 cm (diameter $\times$ length) (Applied Magnets, Plano, TX, USA). The polarization angle varies by 45 degrees between successive cylinders, which are held in place by setscrews (not visible in the figure).

After construction the magnet assembly was measured with a Gaussmeter and Hall-effect probe (F. W. Bell model 5180, Sypris Test and Measurement, Inc., Orlando, FL, USA). These data were used to calibrate the output of our 3D magnetostatic field modeling software (Amperes, Integrated Engineering Software, Winnipeg, Manitoba, Canada). Fig. 2 shows the Amperes output that yields the best fit of the measured data, as determined by the method of least squares. The data appear to be shifted to lower values of x -coordinate compared to the model, possibly indicating a small error in aligning the probe, but the fit is excellent. The Amperes parameters corresponding to this best fit are: coercivity $H_c = -9.63 \times 10^5$ A/m and residual magnetic induction $B_r = 1.15$ T.

With these best fit parameters, the software was used to generate accurate field plots as well as to output data to files, which were used to predict the outcomes of separations. Fig. 3 plots the magnitude of B – shown as color contours – in a cross section at the mid-line of the array. We see that the field is largely constrained to the region above the array. Note that the periodic variation in field along x near the magnet array largely disappears at a z -distance approximately equal to the cylinder radius. On the other hand, the distance from the ends of the array over which the field approaches an almost constant magnitude is relatively small close to the array, but at increasing z this distance increases. For this reason, the magnet array was constructed to be significantly longer than the channel (41.6 cm as compared to the 19 cm channel).

Amperes output enables the calculation of mean B , or $\langle B \rangle$ on various x - y planes as a function of distance from the array, along z . This is shown in Fig. 4. As discussed with regard to Fig. 3, the variation in the magnitude of B decreases with increasing z , and this is shown in progressively smaller standard deviation, as shown by the error bars. A fourth-order polynomial fits the model output well, and the differentiation of this yields the z -component of the gradient, dB/dz , also shown in the figure. The significance of this plot is that magnetic microspheres typically contain a component of superparamagnetic magnetite, and the force on such a particle is given by:

$$F_m = M_m V_m |\nabla B| = M_m V_m \frac{dB}{dz} \quad (1)$$

where M_m is the magnetization of magnetite, which is a function of the local flux density B ; V_m is the volume of magnetite in the microsphere, and $|\nabla B|$ is the magnitude of the gradient of B , the flux density. In this treatment we ignore the contributions of the other materials in the particle, as their magnetizations are relatively small. From the standpoint of separation in the channel, the only component of the gradient of importance is along z , so $|\nabla B|$ becomes dB/dz . The magnetization of magnetite, a non-linear function in B , is also plotted in Fig. 4. This is used to predict the separation outcome, as described later. (For this we use a magnetization curve taken from the literature [10].)

3. Step-SPLITT channel

The step-SPLITT (s-SPLITT) separation device is a ribbon-like channel provided with two inlets and two outlets (see Fig. 5). The channel comprises layers of Plexiglass (PMMA), having dimensions of 19 cm length, 1 cm breadth and either 400 or 650 μm thickness. (In this study we used two different channel thicknesses). Two inlet flows (a' and b') converge at the corner of the “step” and their virtual boundary corresponds to the inlet splitting plane, ISP. A similar outlet splitting plane, OSP, corresponds to the virtual boundary between outlet flows a and b . These are shown by the broken lines in the figure. The transport lamina lies between the ISP and the OSP, and has a thickness δ . It acts as a resistive barrier to transport. The suspension is injected at the inlet labeled a' and a carrier fluid (free of particles) is injected at inlet b' . The sample is axially transported by the flow, while simultaneously, a selective transverse force generated by the magnetic field drives the magnetizable species across the transport lamina and toward the opposite wall.

As mass is conserved, the total and component flow rates are:

$$Q = Q(a') + Q(b') = Q(a) + Q(b) \quad (2)$$

The flow rate of the transport lamina is:

$$Q(t) = Q(a) - Q(a') = Q(b') - Q(b) \quad (3)$$

For separation studies the channel is placed vertically with the inlets at the top. The magnet array is also placed vertically and parallel to the channel at some distance D between the magnet surface and the mid-height of the channel.

The particle suspension contains magnetic microspheres, MM (6.2 μm latex/iron oxide particles, micromod Partikeltechnologie GmbH, Rostock-Warnemuende, Germany), and these were processed alone or in mixtures with non-magnetic microspheres, PS (15.8 μm , 14.9% CV, polystyrene, Duke Scientific, Palo Alto, CA, USA). The particles were analyzed with a Z-2 Particle Counter (Beckman-Coulter, Brea, CA, USA), and their diameter distributions are shown in Fig. 6. The complete resolution between MM and PS allowed precise evaluations of specific particle recoveries and purities in the experiments described below.

The ideal separation would lead magnetic species to elute at the enriched outlet b and nonmagnetic species to elute at the depleted outlet a . Nevertheless, several hydrodynamic

effects including shear-induced diffusion, particle drafting, wall-effects, and even channel imperfections, tend to reduce the quality of separations. Different studies have already been performed for optimizing separations, taking into consideration these effects [7,11]. In this work, we are focused only on characterizing the magnetic field and in showing the capability of the Mg-s-SPLITT to perform continuous open-gradient magnetic separations.

4. Prediction of separations

The magnetic field-induced particle velocity u_{mag} is obtained by equating the magnetic force to the viscous drag opposing migration (from Eq. (1)):

$$u_{mag} = \frac{V_m M_m |\nabla B|}{f} \quad (4)$$

where f where f is the viscous drag coefficient. We can measure u_{mag} in an environment of known field and gradient, such as that of our in-house particle tracking device, the Cell Tracking Velocimeter (CTV) [12,13]. This can be used to predict the magnetic velocity in another environment of known field and gradient, such as our Mg-s-SPLITT. We can write Eq. (4) as a ratio of velocities:

$$u_{mag} = \frac{V_m M_m |\nabla B| f'}{V'_m M'_m |\nabla B'| f} u'_{mag} = \frac{M_m |\nabla B|}{M'_m |\nabla B'|} u'_{mag} \quad (5)$$

The primed variables refer to the environment of the CTV, while the non-primed variables refer to the Mg-s-SPLITT environment. The equation simplifies to the final form on the right when it is assumed that the magnetite volume and drag coefficients are unchanged. The volumetric flow rate traversed by the magnetically migrating particle cloud, as explained in the SPLITT literature [4] is given by:

$$Q_{mag} = b L u_{mag} \quad (6)$$

where b is the breadth of the channel and L is its length. Substituting u_{mag} by Eq. (5) yields:

$$Q_{mag} = \frac{M_m |\nabla B|}{M'_m |\nabla B'|} b L u'_{mag} \quad (7)$$

The CTV system generates data pairs of magnetic velocity increment and frequency. A computer program was written in MapleTM, a computer algebra code (Maplesoft, Waterloo, Ontario, Canada), to read in these data and calculate the relative distribution of particles between outlets a and b , and those encountering the channel wall. This was accomplished using established SPLITT theory [4,14,15] that predicts the fraction of particles exiting at outlets a and b and those encountering the wall ($F(a)$, $F(b)$, and $F(w)$, respectively) as a function of Q_{mag} or u'_{mag} . These incremental recovery outcomes are weighted by the frequency of the input data pair and the results summed to yield overall $F(a)$, $F(b)$ and $F(w)$ for the input particle population. The experimental fractional recoveries are determined from the number of particles recovered at the outlets divided by the number in the feed. In reality, not all of the particles that reach the wall are permanently retained in the channel. Some may roll down the wall and elute in outlet b .

5. Results

The geometric integrity of the channel was first tested by performing a negative control study to evaluate the non-specific crossover of the PS into the enriched outlet. The channel was orientated vertically and no magnet was used. The total flow rate Q was 1.6 ml/min and the flow rate ratios were $Q(a')/Q = Q(a)/Q = 0.5$. Flow components were controlled using a pair of dual syringe pumps (Harvard 33 Twin Syringe Pumps, Harvard Apparatus, Holliston, MA, USA). PS were prepared at a concentration of 2.69×10^6 /ml in degassed 0.1% FL-70 and 50 μ l injected into inlet a' . Under ideal conditions there should be no crossover of particles into outlet b , but as the transport lamina thickness is 0 and the resistance to transport across it vanishes, this is a sensitive method to check for geometric or flow irregularities. Through the use of the Z-2 Particle Counter we evaluated the crossover to be 8.8% of the number fed. 50.1% of the fed particles were recovered in outlet a . This crossover rate was considered to be acceptable [11]. The loss of 50% of the PS particles was due, perhaps, to the relatively high mean sedimentation rate of 7.8 μ m/sec for these particles. The losses would primarily occur in the connecting tubing.

5.1. Pure MM particle studies

These experiments demonstrate the capability of the device to generate a transversal transport of magnetic particles from the inlet a' to the outlet b . The s-SPLITT channel was placed at a distance D of 5.3 mm from the magnet array. Injections of MM were made at different total flow rates Q , while the flow rate ratios were kept constant. The outlet recoveries were determined by evaluating the volume and number concentration (with the Coulter Z-2), and comparing these with the feed. It was not possible to evaluate the fraction retained on the channel wall $F(w)$ experimentally. The theoretical recovery at each outlet was evaluated using the Maple program described above. The red solid theoretical line of Fig. 7 shows that as Q is raised the particles have less time to migrate and are more likely to exit outlet a . This trend is matched by experiment. Likewise, theory predicts there is an optimal flow rate to maximize the recovery in b . Lowering Q allows more particles to cross the transport lamina, but taken too far, too many reach the wall, where they are potentially retained. Experiment corroborates this trend, in spite of the uncertainty of the fate of particles reaching the wall. Both theory and experiment suggest an optimal flow rate of about 2.0 ml/min.

Experiments at constant flow rate but with varying D illustrate a very important feature of this device: the possibility to very easily modify the magnetic force. It is, therefore, possible to adapt the field to suit a wide variety of samples – samples that vary in their interaction with the magnetic field defined by their net dipole moment, equal to $V_m M_m$. Fig. 8 shows the results of this experiment. The theoretical expectation is that increasing D lowers particle magnetophoretic velocity and leaves more particles behind in outlet a . The experimental result agrees remarkably well. We might also expect that low D , for a given Q , could result in a large fraction being retained on the wall, reducing $F(b)$, as we see in the figure. So theoretically, there is an optimal D that maximizes $F(b)$, by minimizing losses to the wall and to outlet a . This occurs at about $D = 10.5$ mm. The trend is only approximately supported by experiment, perhaps because some of the particles that reach the wall at low D eventually roll down the channel and exit outlet b , as seen by a higher $F(b)$ than predicted in this region.

5.2. Binary particle study

The purpose of this experiment was to demonstrate the ability to enrich the magnetic component of a particle mixture of MM and PS. In Fig. 9 the bar graphs show MM purity before and after the separation. The feed (28.0% MM) is enriched to 96.7% purity in outlet

b, while being depleted in outlet *a* to 12.1%. This closely matches theoretical prediction inasmuch as the difference is likely due to the non-specific crossover of PS, which lowers purity. Theoretically, some MM, but not the PS, reach the wall, so the predicted purity at *w* is 100%, although no experimental “wall fraction” could be acquired.

Fig. 10 illustrates the recoveries of the components. In outlet *a*, the MM recovery closely matched the prediction; however, the recovery of PS in this outlet was much lower than predicted. In many practical cases, the separation is performed to collect the magnetic component, while the non-magnetic component is discarded. Yet, the large overall loss of PS is still a concern and will lead to operation changes in future experiments. Outlet *b* shows good agreement regarding the recovery of MM, and we see that compared to outlet *a*, most of the MM were recovered in outlet *b*. Apparently few of the wall fraction eluted in outlet *b*, as the $F(b)$ for MM was lower – rather than higher – than predicted. Few PS crossed over to outlet *b*, close to the prediction of 0%. It was predicted that 58.1% of the MM would reach the wall. The total experimental recovery of MM in outlets *a* and *b* was 33.6%, in contrast to the 41.9% predicted. Here we should mention that the flow rates were not optimal, yet the experiment was still suitable for demonstrating the utility of the device.

6. Conclusions

In conclusion, the Mg-s-SPLITT is very promising and it is easy to control. The magnetic field can be easily modified for specific applications by adjusting the channel position relative to the magnet array. Optimization of this device for specific applications to clinically relevant cell separation is ongoing.

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Fig. 1.
Photograph of the linear Halbach array of diametrically polarized magnet cylinders.

Fig. 2.
Calibration of 3D magnetostatic software using measured data at the array mid-depth.

Fig. 3.
3D simulation of the contours of the magnitude of B around the 16-unit Halbach array. The B values in the legend are scaled by a factor of 10^4 .

Fig. 4.

Mean B and dB/dz on planes as predicted by Amperes software. The planes range from $x = -150$ to $+150$ mm and $y = -10$ to $+10$ mm. The best-fit polynomial of mean B versus z corresponds to $\langle B \rangle = 0.4418 - 0.02112 z + 5.197 \times 10^{-4} z^2 - 7.276 \times 10^{-6} z^3 + 4.420 \times 10^{-8} z^4$. The gradient plot follows from the derivative of the polynomial. Mean B data are used to estimate the magnetization of magnetite.

Fig. 5.
Schematic of the cross-section of the step-SPLITT channel.

Fig. 6.
Particle size distributions of the two particle species used as measured by Z-2 Coulter Counter.

Fig. 7. Recovery of MM as a function of total flow rate. $D = 5.3$ mm; $Q(a')/Q = Q(a)/Q = 0.5$.

Fig. 8.
Effect of D on recovery of MM. $Q = 1.2$ ml/min; $Q(a')/Q = 0.2$; $Q(a)/Q = 0.5$.

Fig. 9.

Evaluation of purity in binary particle mixture. $Q = 1.4$ ml/min; $Q(a')/Q = 0.2$; $Q(a)/Q = 0.4$; $D = 5.3$ mm; total concentration = 8.45×10^5 /ml.

Fig. 10.

Evaluation of recovery in binary particle mixture. $Q = 1.4$ ml/min; $Q(a')/Q = 0.2$; $Q(a)/Q = 0.4$; $D = 5.3$ mm; total concentration = 8.45×10^5 /ml.