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Multistage Magnetic Particle Separator II. Classification of Ferromagnetic Particles

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ABSTRACT

A multistage magnetic particle separator was designed and built. The objective of multistage magnetic separation is the collection of particles in liquid suspension according to their net magnetization. The multistage separator was tested in experiments in which suspensions of an iron-carbon composite particulate in poly(ethylene glycol) were used as feed and in which particles were collected in up to nine fractions according to magnetophoretic mobility. In these experiments particles were aligned in a cylindrical container at a common distance below the top of

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the container by magnetic levitation using a horizontal bipolar "elevator" electromagnet. After the electromagnet was switched off particles were further levitated by a cylindrical permanent "capture" magnet into a capture chamber directly above and in fluid contact with the container in which the particulate was aligned. After a selected period of time (1–20 min) the capture chamber containing particles that were levitated into it was sheared away from the sample chamber. This process can be repeated up to 15 times using capture chambers in a rotating plate. By changing the time period and capture magnet strength each successive capture results in the collection of particles having decreasing net magnetization based on susceptibility of the particulate material and volume of magnetic material per particle. The test material used in this study was a ferromagnetic particulate consisting of an iron-carbon microcomposite. The separation of a heterogeneous particulate suspension into nine subcategories was demonstrated.

Key Words: Microparticles; Magnetophoretic mobility; Separation; Classification; Multistage; Particle separator; Cell separator.

INTRODUCTION

Magnetic particle reagents have become extremely popular as tools in genomics, molecular biology, cell biology, immunology, and stem cell research, to name a few applications. The facilitator of the magnetic reagent market, some $300 million in 2002, is the magnetic particle separator. Magnetic particle separators fall into two classes: binary and proportional separators. Binary separators consist generally of a single permanent-magnet assembly that attracts *all* magnetized particles to a surface, typically a magnetizable, shaped surface near which a high magnetic field gradient is established, and this process is actually called "high-gradient magnetic separation" or HGMS.[1,2] Separation is achieved by entraining nonmagnetic dispersed components in a fluid flow that leaves the attracted magnetic materials immobilized on a surface by magnetic force. All magnetic particles are subsequently collected when the magnetic field is removed. Proportional separators, on the other hand, sort particles according to their net magnetization, M, which is established by the susceptibility, χ, and the volume of the particle. If the fluid in which the particle is suspended is also magnetically susceptible (which all are to some degree), then the magnetic force will depend on the difference in susceptibility, $\Delta\chi$, between particle and fluid materials. To date, a very small number of proportional separators have been presented. These are based on flowing systems with position-sensitive static collection

("magnetaphoresis")[3] or with positioned outlets for the collection of samples of suspended particulate in flow ("magnetophoresis").[4,5]

Unlike electrostatic force, magnetic force depends on absolute field strength as well as its gradient. The absolute field strength induces a magnetic moment in the ferromagnetic particle, and owing to this moment the particle is accelerated in the field gradient. An electric field can be created over very large distances (meters), whereas a reasonably achievable magnetic field and its gradient (see theory, below) become too small to exert a force on micron-sized particles at distances greater than a few centimeters.[6] Therefore, electrophoretic separator designs, such as tall columns[7] and wide, free-flowing fluid planes,[8,9] cannot be implemented in proportional magnetic separations.

A multistage particle collector has been designed, built, and described[10,11] and is used in the current study (Fig. 1). By recognizing the limited geometrical extent of achievable magnetic forces, the equivalent of a tall-column separator is achieved in stages. The basic principle of this type of multistage separator, in general,[12–14] is to levitate separands through the continuous phase over short distances, collect the separated material in the upper-half of a shear cell,[15] and repeat the process until a satisfactory number of fractions has been obtained, or the desired separand is obtained in satisfactory purity. Thus separands are collected in proportion to

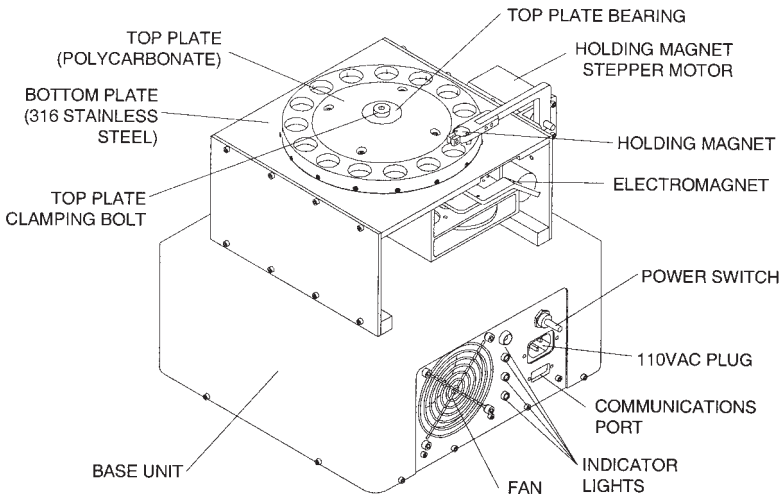

Figure 1. Isometric drawing of the multistage magnetic particle separator studied in this research. "Holding magnet" refers to capture magnets described in text.

the selected property, as in chromatography; in the present case the selected property is net magnetization.

The magnetic particulate chosen for this study is a ferromagnetic composite fabricated by high-energy ball milling of iron particles with activated carbon powder. The resulting composite particles carry the ability to be attracted by an extracorporeal magnet, while a therapeutic agent is adsorbed to the activated carbon component.[16] It is important to note that magnetic reagents used in molecular biology and cell research are normally paramagnetic or superparamagnetic and require the presence of a magnetic field to be magnetized and include materials, such as magnetite, with a fixed value of susceptibility. In the case of ferromagnetic particles, however, susceptibility depends on the magnitude of the applied magnetic field, and remanent magnetization occurs after exposure to a field (the well-known hysteresis effect).

The purpose of this study, therefore, was to examine the ability of multistage magnetic separation to fractionate a ferromagnetic particulate and to characterize parameters that influence separation.

THEORY

Once the elevator magnet is switched off (see Materials and Methods), all magnetic particles are found at vertical position z with z-axis defined downward with the origin at the poleface of a capturing magnet (Fig. 2). A force balance on a levitated particle will then be

$$m\left(\frac{d^2z}{dt^2}\right) = F_g - F_b - F_d - F_m \tag{1}$$

in which subscripts g, b, d, and m correspond to gravitational, buoyant, drag, and magnetic forces, respectively. Under the conditions of experimentation, residual inertial acceleration can be neglected, since viscous drag dominates particle motion, and terminal velocity is reached instantaneously. Reynolds' number is less than 10^{-4} for these particles. Terminal velocity v is constant, so

$$\frac{d^2z}{dt^2} = 0.$$

Thus substituting the usual relationships for Stokes' sedimentation and the z-component of the magnetic force[3,6] (Reddy et al., 1996) given by

$$F_m = -V\Delta\chi B(dB/dz)/\mu_o \tag{2}$$

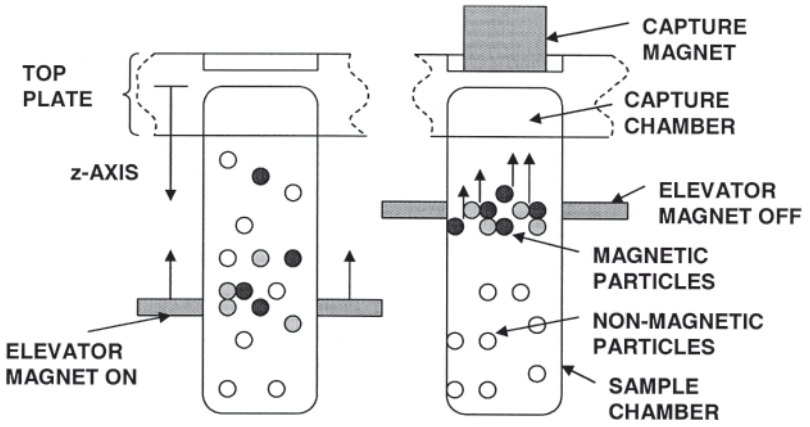

Figure 2. Two steps of particle capture in a single stage of the multistage magnetic particle separator. Left: The elevator magnet positions magnetic particles (black and gray circles) at a specified vertical location in the sample chamber by moving upward while energized, while non-magnetic particles (white circles) are not moved and sediment in the sample chamber. Right: The capture magnet is brought into place, leading to upward movement of magnetic particles from the final elevator position at velocity determined by their individual magnetophoretic mobility (upward arrows). Capture is completed by the sideways movement of the capture chamber after interval Δt.

where $V =$ particle volume, $B =$ strength of magnetic field (Teslas, T) at position z, $\Delta\chi =$ relative volumetric magnetic susceptibility (particle minus solvent), and $\mu_o =$ magnetic permeability of free space ($4\pi \times 10^{-7}$ T-m/A), gives the net vertical velocity

$$v = \frac{d_p^2(\rho_p - \rho_s)g}{18\eta} + \frac{d_p^2 \Delta\chi}{18\eta\mu_0} B \frac{dB}{dz} \tag{3}$$

where ρ_p and ρ_s are, respectively, the density of particle and fluid, d_p is particle diameter, and η is the dynamic viscosity of the suspending fluid. Or

$$v = \frac{dz}{dt} = v_s - v_m \tag{4}$$

where v_s is the gravitational sedimentation velocity, and v_m is the velocity due to the magnetic field in the absence of gravity. Note that v_m is negative (upward) because in this coordinate system dB/dz is negative (B decreasing with increasing z in the downward direction).

Thus the velocity of levitation of a magnetic particle will depend directly on its relative volumetric susceptibility $\Delta\chi$ and the magnetic driving, or

ponderomotive (mass-moving), force $B(dB/dz)/\mu_o$. It is traditional to characterize quantitatively a material moving in a field by its *mobility*, defined as the ratio of velocity to ponderomotive force, thus the magnetophoretic mobility is defined as

$$\mu_m = \frac{v_m}{B(dB/dz)} \tag{5}$$

This quantity can be used to determine particle characteristics, since it is apparent from Eqs. (3–5) that

$$\mu_m = \frac{d_p^2 \Delta\chi}{18\eta\mu_0}. \tag{6}$$

Conversely, from basic particle data it is possible to calculate the magnetic field required to achieve a particular particle velocity. However, although the magnetophoretic mobility is a constant the ponderomotive force depends on the position of the particle with respect to the magnet. For a cylindrical permanent magnet of radius R, length L and central poleface field B_o, the on-axis field B as a function of distance z from the poleface is given by[17]

$$B = \frac{B_o}{2}\left[\frac{L+z}{(R^2+(L+z)^2)^{1/2}} - \frac{z}{(R^2+z^2)^{1/2}}\right]. \tag{7}$$

This relationship applies to an isolated magnet; however, in the multistage magnetic separator there are many possibilities for distorting magnetic flux lines owing to the presence of ferrous metals, motors, the elevator magnet, etc. Therefore an empirical relationship was determined on the basis of measurements of the magnetic field of each permanent magnet, and a satisfactory description of the on-axis field was found to be given by

$$B = AB_o e^{-kz} \tag{8}$$

where A is a fraction (<1) of the poleface field at the chosen position of measurement, and k is an empirically determined coefficient. Both AB_0 and k are determined from a fit of Eq. (8) to empirical data.

Due to the changing field as each particle approaches the capture magnet poleface the particle velocity is not constant, so, after substituting v_m according to Eq. (4), Eq. (5) becomes

$$\mu_m = \frac{(dz/dt) - v_s}{B(dB/dz)}, \tag{9}$$

where the sign of Eq. (9) has been purposely changed to force μ_m positive.

Separating variables and integrating Eq. (9) over the time interval of exposure to the capturing magnetic field Δt results in Δt equating to an integral in z having the following standard form with its analytical solution (Burington, 1948):

$$\int \frac{dz}{b + ce^{az}} = \frac{1}{ab}[az - \log(b + ce^{az})] \tag{10}$$

where $b = v_s$, $ce^{az} = \mu_m B(dB/dz)$ as substituted from Eq. (8).

Two significant simplifying assumptions have been included in this theory. In the case of particle properties, a constant value of $\Delta\chi$ has been assumed for the iron component of the composite particles; this is an inexact assumption for ferromagnetic particles. In the case of the ponderomotive force, Eqs. (7) and (8) are one-dimensional and do not account for the radial gradients in the magnetic field, and hence the radial component of the magnetic force vector is ignored.

MATERIALS AND METHODS

Multistage Magnetic Separator

The engineering details of the multistage magnetic particle separator used in these studies have been described previously.[10] An isometric view of the unit used for this research is shown in Fig. 1. The steps involved in the operation of a single stage are summarized in Fig. 2, where it is shown that randomly dispersed particles are gathered into a zone at a specified vertical position in the sample chamber by the elevator magnet. As soon as this occurs the elevator magnet is switched off, and a permanent magnet is positioned over the capture chamber. This permanent magnet draws particles from the starting position toward the capture chamber according to their magnetophoretic mobility. After interval Δt the upper (capture) chamber is moved sideways to trap the collected particles. This process is repeated up to 15 times in the device used in this study. The top plate contains 15 capture chambers.

To operate the elevator magnet that aligns magnetic particles at a common level in the sample chamber, two variables were programmed into the graphical user interface: the speed of the elevator motor and the current applied to the electromagnet. The speed of elevation had a range of 0.12–0.25 mm/s and a current range on the magnet coil giving field strengths from 1 to 25 mT at the center or at the wall of the sample chamber as shown in Fig. 3.

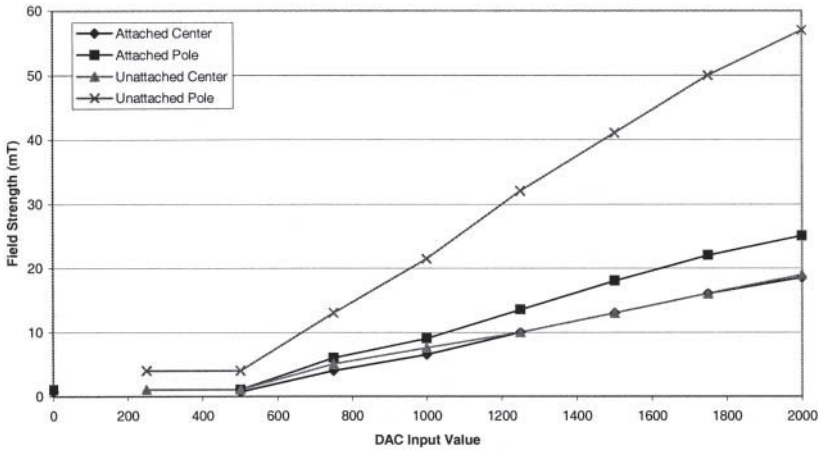

Figure 3. Magnetic fields associated with operator-input values for the elevator magnet (calibration curves). Fields were measured, in mT, in the center of the sample chamber and at the chamber wall nearest a magnet pole. DAC = Digital-to-analogue converter setting display. The DAC input value is the number entered by the user to adjust the field strength of the elevator magnet. "Attached" and "unattached" refer to the positioning of the Hall-effect sensor with which the measurements were made.

All operations of the multistage magnetic particle separator are controlled by a graphical user interface (GUI) programmed using C ++ Builder® for the MS-Windows® environment. A typical screen display is shown in Fig. 4, which can be compared to Fig. 2. An animated diagram of the sample chamber, capture chamber, elevator magnet, top and bottom plates and capture magnet is displayed. The color of each displayed component tells the user that this component is "on" or "off" during automated operation. The elevator magnet in the display travels up and down as the actual elevator magnet travels, and the upper plate is shown rotating in the display as the actual upper plate rotates and moves each capture chamber to its next position. The tools displayed on this screen were used to establish the settings in Table 1, for example.

Ferromagnetic Particles

Iron-carbon particles were used in this research. They are produced by a proprietary high-energy ball-milling process in which iron particulate is combined with powdered activated carbon. The average ratio of carbon to

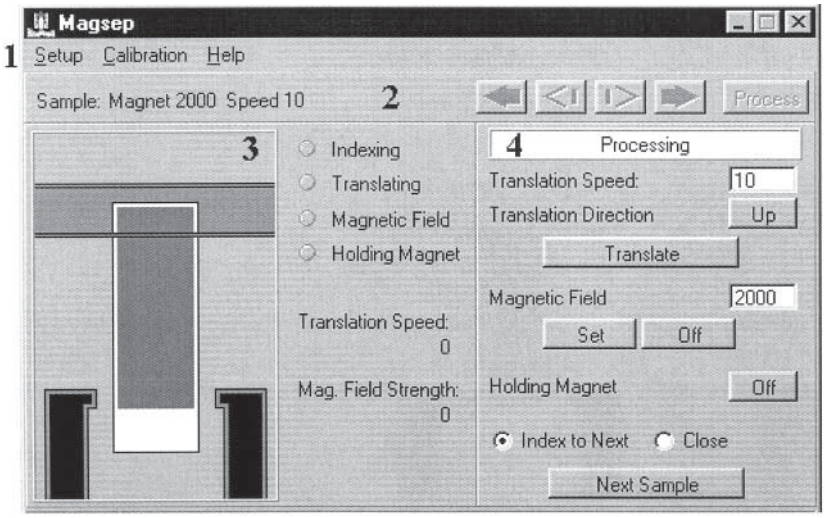

Figure 4. Screen display of graphical user interface (GUI) showing (1) drop-down menus, (2) display of elevator magnet parameters and "manual" top plate operating arrows, (3) graphical representation of top plate and elevator magnet positions and movement (animation), and (4) display of user-programmed parameters and controls.

iron is established by parameters of this fabrication procedure. For the current study, a test lot of particulate produced in August 1998 and sieved at 20 μm was used within 1 week of dry storage after production. These were strictly experimental particles fabricated only for separations

Table 1. Experimental parameters for a nine-stage test classification of ferromagnetic particles (used to obtain data of Fig. 6).

	Elevator magnet			
Stage	Speed (mm/s)	Field (mT)	Time interval (min)	Capture magnet field, B_0 (mT)
1	0.147	19	3	57
2	0.147	19	1	85
3	0.147	19	3	89
4	0.147	19	1	89
5	0.147	19	1	90
6	0.147	19	3	91
7	0.127	22	1	93
8	0.120	24	1	102
9	0.120	24	3	107

testing and not for therapeutic research. To prevent excess exposure to water and the possibilities of corrosion and/or aggregation, particulate was typically suspended in poly(ethylene oxide), also known as., poly(ethylene glycol) with average molecular weight of 400 (PEG-400) and viscosity = 106.9 cP. The sample chamber was filled by combining 0.75 mL of a 0.5% suspension of particulate in PEG-400 and adding 2.6 mL of PEG-400.

The net magnetization, and thus the mobility, of each particle in a magnetic field depends on its relative volumetric susceptibility, $\Delta\chi$, i.e., the difference between its susceptibility and that of the suspending fluid. Since the susceptibility of magnetically saturated iron is in the +400 range (ferromagnetic) and that of the solvent (a diamagnetic organic oxide) is in the -10^{-5} range,[18] the latter is neglected. However, the carbon component of each particle, with a susceptibility of -4×10^{-4} [18] decreases the net magnetization of each particle according to the volume fraction of carbon in each particle. Therefore magnetic sorting is expected to separate iron-carbon composite particles according to size and iron content.

Multistage Classification Testing

The effects of instrument variables on ferromagnetic particle capture were evaluated. Nine stages were used with the settings given in Table 1. These setting were programmed using the graphical user interface (GUI). Collection chambers 1–9 were filled with PEG-400, and fill-port plugs were threaded into place allowing excess PEG to escape through the fill-port vent (a slot in the fill-port thread). The sample chamber was filled with 0.75 mL of 0.5% suspension of the particles in PEG-400 and topped up with 2.6 mL of PEG-400. The program (Table 1) was initiated, and the elevator magnet translated upward while switched on, with its motion displayed on the GUI screen (Fig. 4). After the elevator reached its programmed elevation (7 mm below the interface) the program switched off the magnet and notified the operator to install the permanent capture magnet for stage 1. After the programmed capture interval the top plate rotated to place the next capture chamber above the sample chamber while the elevator returned to its home position surrounding the sample chamber. The elevator magnet repeated its cycle to initiate the next repetition of the process, which was repeated nine times. Particles were collected from each capture chamber using a syringe and needle and counted using a hemacytometer at 600× magnification and subjected to size analysis by forward-angle light extinction using a Model 770 Accusizer (Particle Sizing Systems, Inc., Santa Barbara, CA) producing differential and cumu-

lative size and volume distributions. About 200,000 particles are counted per distribution, and the Accuziser does not include particles below approximately 0.4 μm in diameter.

RESULTS AND DISCUSSION

Magnetophoretic Mobility for a Stage

As an example, the magnetophoretic mobility corresponding to a stage served by an 85 mT magnet was determined as follows. First the magnetic field profile of the 85 mT magnet was determined as a function of distance from the top of the capture chamber, and this is shown in Fig. 5. The best-fit parameters of Eq. (8) were determined from these data (using the "Trendline" command in Microsoft Excel®), giving

$$B = 34.4\mathrm{e}^{-0.215z}$$

where z is the distance from the top of the cavity. The sedimentation velocity of iron-carbon composite particles was found to be $v_s = 2.6 \times 10^{-6}\,\mathrm{m/s}$, and a constant magnetic susceptibility (for unsaturated iron) was assumed. The particles' starting position was at $z = 10.5\,\mathrm{mm}$, and the level at which they are captured is $z = 3.5\,\mathrm{mm}$, therefore these become the distance integration limits. Substituting these relationships into Eq. (9) and integrating over a 60-s interval from $z = 10.5$ to $z = 3.5\,\mathrm{mm}$ according to the procedure for using Eq. (10) and solving for the (experimentally determined) mobility yields $\mu_m = 0.0136\,\mathrm{mm^2 mT^{-2} s^{-1}}$ or, in more readily understood units, mm/s per

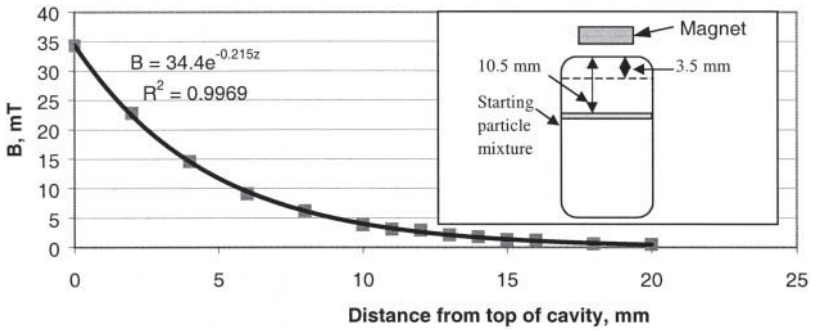

Figure 5. On-axis magnetic field map for an 85 mT cylindrical magnet. Inset: Geometry of magnet and upper and lower chambers of the apparatus. Dashed line represents the liquid–liquid interface (see Fig. 2).

mT^2/mm. Thus, for each capture magnet size and each selected capture time interval, a magnetophoretic mobility is calculated for each stage of the multistage magnetic separator. Using this mobility to calculate v_m, the velocity of the particle due to magnetic force only, reveals that initially (at the starting level in the sample chamber) $v_m = 4.2 \times 10^{-6}\,m/s$, which is less than twice v_s, and finally, at the capture level $v_m = 8.7 \times 10^{-5}\,m/s$, which is more than 30 times v_s. This result emphasizes the importance of using Eq. (9) in mobility calculations so that both v_s and dB/dz and their dependence on z are correctly incorporated.

Non-magnetic Spontaneous Particle Transfer

It is assumed that some particles will be transferred "spontaneously" into the capture chamber from the sample chamber as a result of being at the top of the sample chamber at the time of sliding the capture chamber sideways. This process has been studied for other shear-cell systems in the past,[15] and it is known that some liquid is mixed into the opposing chamber at the sliding fluid interface. Twelve experiments were performed in which a lower cavity was filled with a suspension of iron particles ($0.033\,\mu g/mL$) in EtOH, and upper cavities filled with EtOH were swept over them. The particle concentration in the upper cavity was determined by hemacytometer counting, and it was found that there was a $1.82 \pm 1.74\%$ loss from bottom chambers due to particle spontaneous transfer between the lower and the top plate chambers. Despite differences in particle density and fluid viscosity this finding is in reasonable agreement with transfers found in other systems.[15]

Multistage Classification Test

The protocol described here and in Table 1 was followed using the iron-carbon composite particulate. The resulting particle counts for each stage are given in Fig. 6. The first capture step had very few particles, and the size distribution of the particles was very similar to that of the starting material. Therefore it was determined that the 57 mT magnet was too weak to capture particles in 3 min, that essentially no particles had adequate magnetophoretic mobility to be captured, and that the particles that were transferred were transferred by fluid mixing at the interface as described in the previous paragraph. The highest-mobility (and largest—see Fig. 7) particles were captured in stage 2 at the 85 mT magnet. The parameters at stage 4 (same magnet as stage 3) were chosen to show that particles with a magnetophoretic mobility above this cutoff had all been captured at stage 3. The results in Fig. 6 do in fact

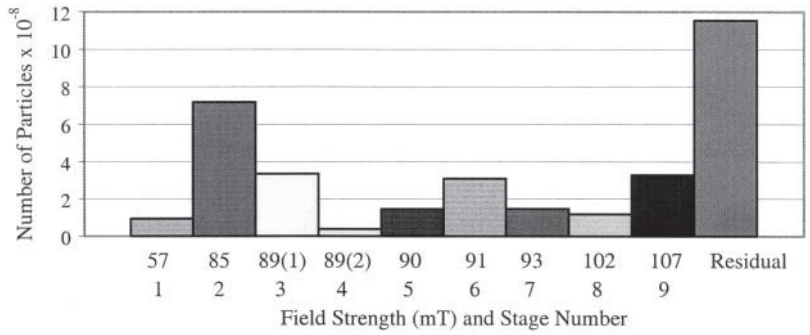

Figure 6. Number of particles found in each stage of the multistage magnetic separator using settings described in Table 1. Particles were counted by hemacytometer.

show that stage 4 captured very few particles. The slight increase in field from stage 4 to stage 5 mobilized those particles at the elevator-magnet level not reached by the stage 4 magnet. Stages 5, 6, and 7 represent very little change in ponderomotive force, but the capture time was three times as long in stage 6 (see Table 1). The fact that stage 6 captured the most particles in this group is further evidence that particles are selected on the basis of their rate of migration to the fluid interface from the starting position established by the elevator. Stages 7, 8, and 9 were operated at higher elevator magnet fields and slower elevator speeds, and stage 9 used the longer capture

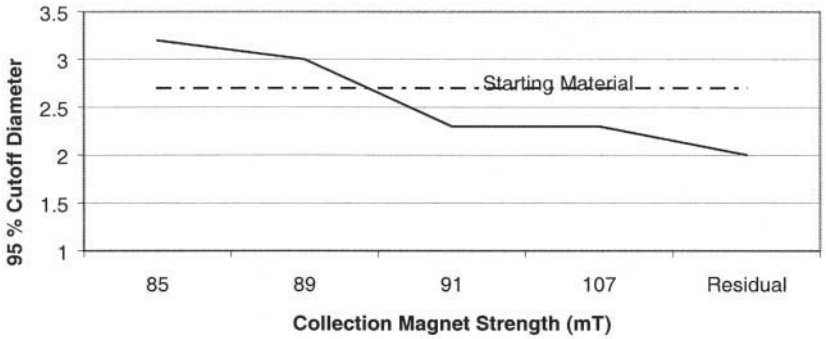

Figure 7. Ninety-five percent cut-off diameter of particles collected in each stage shown in Fig. 6. Stage number corresponding to each capture magnet field is given on abscissa of Fig. 6. Size distributions were determined by Accusizer. The integral size distribution of each sample was analyzed to determine 95th percentile particle diameter (95% cutoff diameter).

interval of 3 min, all to determine if additional weakly magnetic particles could be captured. The rise of particle number with increasing fields in both the elevator and capture magnets is consistent with the existence of a significant low-mobility particle population. The residual suspension, particles remaining in the sample chamber, represented nearly one-third of the counted particles. These were all below the lowest magnetophoretic mobilities that could be captured and possibly not sufficiently magnetic to be moved by the elevator magnet despite its proximity to the particles in the sample. These particles were observed visually to remain at the bottom of the sample chamber during elevator magnet operation, and essentially all of these residual particles were less than 2.0 μm in diameter (Fig. 7).

Classification by Size

The size distributions of particles in each fraction were qualitatively consistent with their magnetophoretic mobilities. As inferred from Eq. (6), particles with a constant $\Delta\chi$ can be classified according to their diameter using magnetophoretic mobility as the classifying variable. Figure 7 shows, for each fraction, the diameter at which 95% of the particles in the collection have a smaller diameter than the value on the ordinate. It can be seen that low magnetic field strengths capture large particles, whereas high magnetic field strengths capture the smaller particles. This is in concurrence with Eq. (6) for magnetophoretic mobility. At low magnetic field strengths, particles with high magnetophoretic mobilities will be captured. Particles with high magnetophoretic mobilities, at constant $\Delta\chi$, will correspond to large particles (greater total amount of Fe). It can also be seen in Fig. 7 that it is possible to enrich for large or small particles. In this experiment, stages 2 and 3 were enriched for large particles, and stages 6 and 9 were enriched for small particles. Using the multistage separator to enrich for large particles is not as ideal as other methods due to the fact that early stages will not only capture large particles but also will capture aggregates that may have formed due to magnetization if the particle concentration is high.[6,19] The multistage separator may be better used to enrich for small particles or to separate particles which do not meet the standards of magnetophoretic mobility for a specified application.This could be done by setting the lowest magnetophoretic mobility allowed for the application by selecting a large magnetic field and/or a long dwell time. The large magnetic field strength should be at a late stage in a multistage process, where magnetic field strengths are stepped up to the highest value. In the population of particles studied, both size and $\Delta\chi$ were distributed variables; in particle populations with uniform $\Delta\chi$ the multistage process will serve as a sorter according to size.

CONCLUSIONS

An automated multistage magnetic separator was tested in the classification of ferromagnetic iron-carbon composite particles suspended in poly(ethylene glycol). Calculations were performed for the empirical determination of magnetophoretic mobility using simplifying assumptions, and particle migration velocities were predicted. Particles were collected in fractions according to their magnetophoretic mobility, which is a function of particle size and iron content.

NOMENCLATURE AND ABBREVIATIONS

A	fraction (<1) of the poleface field
B	strength of magnetic field (Teslas, T)
B_o	central poleface magnetic field, T
D	particle diameter (μm)
F_g, F_b, F_d, F_m	forces on a particle in which subscripts g, b, m, and d correspond to gravitational, buoyant, magnetic, and drag forces, respectively,
k	empirically determined exponential coefficient (mm^{-1})
L	magnet length (cm)
m	particle mass (g)
R	magnet radius (cm)
Re	Reynolds' number
t	time (s)
V	particle volume (μm^3)
v	particle terminal velocity ($mm\,s^{-1}$)
v_m	velocity due to magnetic field in the absence of gravity ($mm\,s^{-1}$)
v_s	gravitational sedimentation velocity ($mm\,s^{-1}$)
z	vertical distance variable, distance from top of cavity (mm)
d^2z/dt^2	net inertial acceleration of particle in z direction ($mm\,s^{-2}$)
$\Delta\chi$	difference in susceptibility between particle and fluid
η	dynamic viscosity of suspending fluid ($g\,cm\,s^{-1}$)
μ_o	magnetic permeability of free space ($4\pi \times 10^{-7}$ T-m/A)
μ_m	magnetophoretic mobility ($mm^2\,T^{-2}\,s^{-1}$)
ρ_p and ρ_s	density of particle and fluid, respectively ($g\,cm^{-3}$)
MTC	magnetically targeted carriers
PEG	Poly(ethylene glycol)

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