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Rapid and Large-Scale Separation of Magnetic Nanoparticles by Low-Field Permanent Magnet with Gas Assistance

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Significance

Bubbles can be used to greatly improve the speed of magnetic separation (MS) and overcome the limitation of magnetic force on the capture distance, making low-field MS highly efficient and easily scalable. This novel method leads to the development of a medium-free continuous gas-assisted magnetic separator on small pilot scale using low-field permanent magnet. This separator is demonstrated highly efficient for recovery of proteins-loaded magnetic nanoparticles from large volume biosuspension. © 2014 American Institute of Chemical Engineers *AIChE J*, 60: 3101–3106, 2014

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Due to the more selective and efficient removal of particles from solution with external magnetic fields than centrifugation or filtration, magnetic separations (MSs) have been widely used in many areas, such as biotechnology, water treatment, and ore refinement.[1,2] Central to the process is the generation of magnetic force on particles large enough to overcome competing forces, such as hydrodynamic drag force, diffusional force, and gravitational force. According to the general relationship for magnetic force (F_m) on a particle,[3] F_m is proportional to the particle volume, magnetic flux density, and the gradient.

Magnetic nanoparticles have very high available adsorptive areas to volume ratio and superparamagnetism (below the size of 30 nm). These advantages make them ideally suited for use in MS technology. Easy recovery of these nanoparticles from suspensions is central to their application. Especially, to their applications in bioseparation and water treatment with the aim of the product or purification, easy separation of them from large volume suspensions is very important.

In terms of the possibility of separation, theoretical predictions based on extrapolations from the bulk material confirm that the critical size of an isolated iron oxide particle for separation is about 50 nm at extremely high field and high gradient.[3,4]

Additional Supporting Information may be found in the online version of this article.

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Surprisingly, Colvin and coworkers[5] have recently demonstrated the possibility of separation of monodisperse nanoparticles with the size larger than 10 nm by a low-field permanent magnet. The reason for the successful separation is reversible aggregation of nanoparticles in an external magnetic field.

This low-field mode avoids not only the use of expensive electromagnet, even superconductive electromagnet[6,7] for high field but also the use of complex expensive device of high-gradient magnetic separator (HGMS) for high gradient. More importantly, the most favorable combination of a nanodispersion and easy recovery with a low-field permanent magnet can be carried out. These advantages are very fascinating for MS technology.

However, rapid separation of magnetic nanoparticles in this low-field mode is difficult. The reason is that magnetic nanoparticles with very small volume generally suffer from very small magnetic force in a low-field gradient. Furthermore, low-field MS speed decreases with the decreasing size and concentration of particles, because the formation of field-induced aggregates becomes increasingly difficult under these conditions.[8]

Bigger difficulty exists in low-field recovery of magnetic nanoparticles from large volume suspensions, because MS scale is badly limited by the requirement of short distance between nanoparticles and source magnet. Magnetic force on a particle is known to be very sensitive to the distance, for example, the magnetic force in HGMS diminishes with the cube of the distance.[4] Thus, MS occurs only in a short distance range. This is especially the case for low-field MS of nanopartilces. Furthermore, the scale-up of continuous or batch magnetic process generally leads to the increase of the capture distance. This makes low-field MS feasible only for very small volume suspensions. The application of larger scale separation is required to use higher field and higher gradient to offset the decreasing magnetic fore with the increasing distance.

For MS solely relying on magnetic force, partially overcoming these difficulties remains highly dependent on resulting large magnetic force from high field, high gradient, and even larger magnetic bead with high magnetization which is usually prepared by complex bead technology.[9,10] However, if an additional external force is exerted on the nanoparticles to fuel the MS process and to overcome the limitation of magnetic force on the capture distance, rapid and easily scalable separation of magnetic nanoparticles by low-field permanent magnet may be feasible.

The capture of particles by rising bubbles is the central process in froth flotation, an efficient solid-liquid separation technology widely applied for mineral ores, plastics, coal, and so on.[11,12] The principle of this process is that the action forces of bubbles on particles overcome the opposing forces on them, leading to the motion of particles toward foam phase, and therefore, attaining remote capture and concentration results.

Herein, we report low-field MS technology assisted with an external force, the force of bubbles on particles. Having previously established that the 10-nm citrate-modified magnetic Fe_3O_4 nanoparticles (CMNs) with bovine serum albumin (BSA) loading could be concentrated by rising bubbles without additional detergent,[13] we here show that these proteins-loaded nanoparticles can be rapidly and remotely removed from dilute solution by gas-assisted low-field MS. To determinate whether surface properties limitation of nanoparticles exists for this separation process, we use CMNs with different amount of BSA adsorption as different flotability examples and 10-nm hydrophilic Fe_3O_4 nanocrystals as no flotability example. We also show that all of these nanoparticles can be rapidly and remotely removed as well. Based on this novel method, we further design a continuous gas-assisted magnetic separator on small pilot scale using low-field medium-free permanent magnet, and use this separator for larger scale recovery of BSA-loaded CMNs from dilute solution, as an efficient example of biotechnology application.

BSA-loaded CMNs could be rapidly and remotely removed from solution by a hanging low-field (the maximal field of 0.2 T) magnet with bubbles assistance. In a flotation column with this magnet, shown in Figure 1a, the maximal distance separated by this magnet without bubbles was only 42 mm. Once nitrogen starts bubbling, the solution within the distance of 267 mm in the whole column quickly became clear (Figure 1b). Similar capture with greater distances could be observed for the solution loading more volume of feedstock. The contrast of separation rate in MS and gas-assisted magnetic separation (GAMS) (Figure 1c) shows that the separation rate in GAMS is much faster than that in MS, which interestingly increases with the increasing distance. Figure 1d confirms that much faster speed in GAMS at 0.1 T can be obtained than that in MS at 0.4 T. Furthermore, GAMS's preponderance in the separation speed over MS can be further expanded with increasing gas flow rate (Figure 1e).

The removal of the BSA-loaded CMNs can be explained by the forces analysis of particles in GAMS (shown in Supporting Information Figure S1). In this process, the principle of MS becomes

$$F_{\text{b-p}} + F_{\text{m}} > F_{\text{d}} + F_{\text{v}} + F_{\text{g}} \tag{1}$$

Where $F_{\text{b-p}}$ is force of bubbles on particles, F_{d}, F_{v}, and F_{g} denote diffusion force of particles, fluid drag force, and gravity force, respectively. In the capture region of the hanging magnet, particles suffer from both $F_{\text{b-p}}$ and F_{m} in the same direction, while beyond the region, only $F_{\text{b-p}}$ act on them. In terms of the possibility of remote capture, BSA-loaded CMNs could be remotely captured by rising bubbles without extra detergent.[13] These capture facts without magnetic field show that the forces of bubbles on particles are large enough to overcome those opposing forces on them, namely

$$F_{\text{b-p}} > F_{\text{d}} + F_{\text{v}} + F_{\text{g}} \tag{2}$$

Clearly, even for very low magnetic force, the inequality (1) is satisfied, meaning the feasibility of remote separation. In this long-distance capture, the requirement for magnetic field is to retain those floated particles at its surface to prevent them from returning to the solution. Thus, the requirement of magnetic field in GAMS is very low, because nanoparticles suffer from maximal magnetic force at the surface of the magnet at given field, but less competing forces to be overcome, such as diffusive force and hydrodynamic force caused by liquid surface disturbance.

In terms of separation speed, rapid separation of nanoparticles at low field can be obtained by bubbles assistance. In GAMS process, the particles captured by bubbles rise rapidly together with the bubbles in the particle-bubble aggregates,

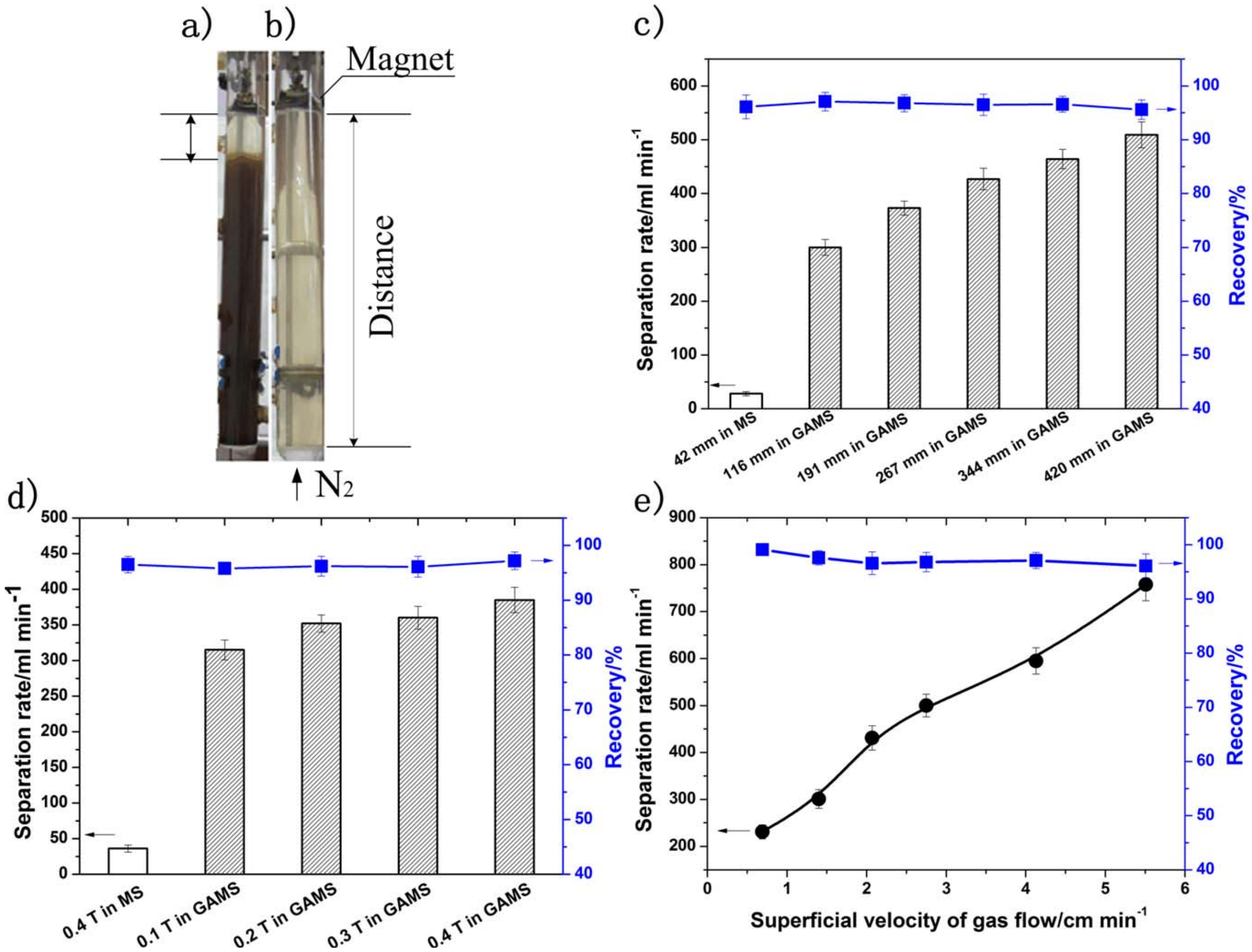

Figure 1. (a) MS at 0.2 T. (b) GAMS at 0.2 T. (c) The effect of the distance between nanoparticles and hanging magnet on separation efficiency in GAMS. (d) Comparison of separation efficiency in GAMS at various field strength and in MS at 0.4 T. (e) The effect of gas flow rate on separation efficiency in GAMS.

Unless otherwise stated, experiment conditions for (a), (b), (c), (d), and (e) are: CMNs concentration, 0.5 mg mL^{-1}; pH, 4.8 (0.02 M acetate buffer); BSA amount on CMNs, 149.2 mg g^{-1}; superficial velocity of gas flow, 1.72 cm min^{-1}; magnetic field, 0.2 T; the distance from the magnet, 191 mm by loading 250-mL solution. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

and then are enriched into the capture region of magnetic field, finally are further accelerated by the magnetic force. Furthermore, the concentrated solution of nanoparticles is available for the rapid capture of nanoparticles by magnetic field due to easy formation of nanoparitcles aggregates.[8] In GAMS, the capture of bubbles on particles is the rate-controlling step of separation rate of particles, while the capture rate of bubbles on particles badly depends on gas flow rate and the capture efficiency of bubbles on particles in flotation process. Therefore, MS rate can be further accelerated by increasing gas flow rate. Interestingly, the speed also increases with the increasing distance of particles from source magnet due to higher capture efficiency of bubbles on particles with the increasing distance (increasing loading volume).

It is important that rapid and remote capture in GAMS can be obtained not only for hydrophobic nanoparticles with good flotability but also for hydrophilic nanoparticles with poor flotability. To determinate whether surface properties limitation of particles exists for this separation method, we use hydrophilic CMNs with different amount of hydrophobic BSA adsorption as different flotability examples. Flotation experiment results in Supporting Information Figure S2 showed that flotability of these particles decreased with decreasing BSA amounts on CMNs, and no flotability for no BSA-loaded CMNs. Further measurement of contact angle of these particles in Supporting Information Figure S3 showed also that the hydrophobicity of CMNs increased with increasing BSA amounts on CMNs. The separation results of GAMS for these particles are shown in Figure 2a. Good remote recovery (191 mm over the maximal distance of 42 mm at 0.2 T) of all particles can be achieved at 0.2 T field in GAMS, and the separation rate decreases with decreasing flotability of particles.

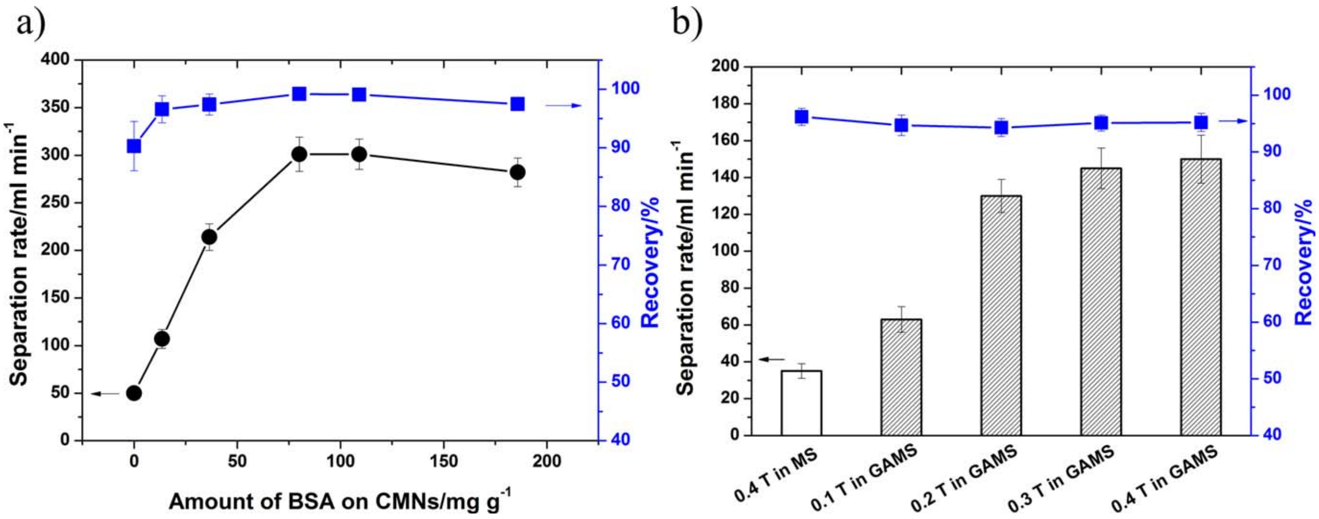

Figure 2. (a) Batch GAMS of magnetic nanoparticles with different flotability, experiment conditions: CMNs concentration, 0.5 mg mL^{-1}; pH, 4.8 (0.02 M acetate buffer); superficial velocity of gas flow, 1.72 cm min^{-1}; magnetic field, 0.2 T; the distance from the magnet, 191 mm by loading 250-mL solution. (b) The contrast of separation efficiency between MS at 0.4 T and GAMS at various field strengths for 10-nm Fe_3O_4 nanoparticles, experiment conditions: Fe_3O_4 concentration, 0.5 mg mL^{-1}; pH, 6.0; superficial velocity of gas flow, 2.07 cm min^{-1}; the distance from the magnet, 191 mm by loading 250-mL solution.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

But even for no BSA-loaded CMNs with no flotability, the separation rate in GAMS is still faster than that in MS at 0.2 T (50 mL min^{-1} in GAMS to 30 mL min^{-1} in MS). To further demonstrate that for hydrophilic nanoparticles, GAMS has also faster rate at lower field than MS, the 10-nm magnetic Fe_3O_4 nanoparticles (the micrograph of Transmission Electron Microscope, Supporting Information Figure S4) with strong hydrophilicity are selected. The separation results are shown in Figure 2b. As expected, the higher speed by GAMS at 0.1 T and 191 mm distance can be gained than that by MS at 0.4 T and 48 mm of maximal distance.

The reason for this can be same explained from the forces analysis in flotation process. According to flotation mechanism, the acting forces between bubbles and particles in flotation process include mainly hydrodynamic forces in collision process, and hydrodynamic forces and hydrophobic forces in attachment process. Among these forces, hydrophobic forces determine the occurrence of bubble-particle attachment, further the flotability of particles. For hydrophilic particles, the hydrodynamic forces between bubbles and particles still exist in short contact time between their collision and separation process. This contact time includes collision time in collision process and sliding time of particle around a bubble in attachment process.[14–17] These hydrodynamic forces not only cause a rising motion of particles in this contact time but also provide particles with kinetic energy fueling the continued motion of particles in a limited distance after bubbles are separated with particles. In other words, these forces can be treated as the equivalent inertial force of bubbles acting on particles in a short time. This inertial force can overcome the opposing forces, causing the capture of bubbles on particles in a limited distance. Therefore, it is possible that the remote capture of bubbles on hydrophilic particles occurs by one or more times of this collision contact process. In terms of separation speed, lower speed in GAMS is achieved for hydrophilic particles than for hydrophobic particles, because the collision process without the attachment will decrease the capture efficiency of bubbles on hydrophilic particles. But rapid capture of them is still feasible, because the decrease of speed can be partly compensated by increasing gas flow rate.

The force of bubbles on particles, as an external force, can be used to fuel MS and to overcome the limitation of magnetic force on the capture distance. This makes low-field MS process easy and simple. Gas-assisted low-field MS now makes it possible to develop easily scalable, highly efficient, and continuous MS process with low cost for the recovery of magnetic nanoparticles. A novel continuous gas-assisted magnetic separator on small pilot scale is designed using low-field medium-free permanent magnet and its schematic diagram is shown in Figure 3a. The predispersed solution of particles is transported into the flotation column, via peristaltic pump. Magnetic nanoparticles in the solution are rapidly captured by rising bubbles, and enriched at the top of solution, then removed out of the solution by a magnetic roller with a scraper blade. The effluent from the bottom of the flotation column is adjusted via an overflow pipe to keep the proper contact of the magnetic roller with liquid level. The key component in this magnetic separator is shown in Figure 3b. The magnetic roller, in which the surface maximal magnetic flux density is conservatively designed as 0.4 T using permanent magnet, is driven by variable speed motor to adjust the removal rate of particles from the solution.

We explored whether this separator could be used for large-scale continuous and batch recovery of BSA-loaded

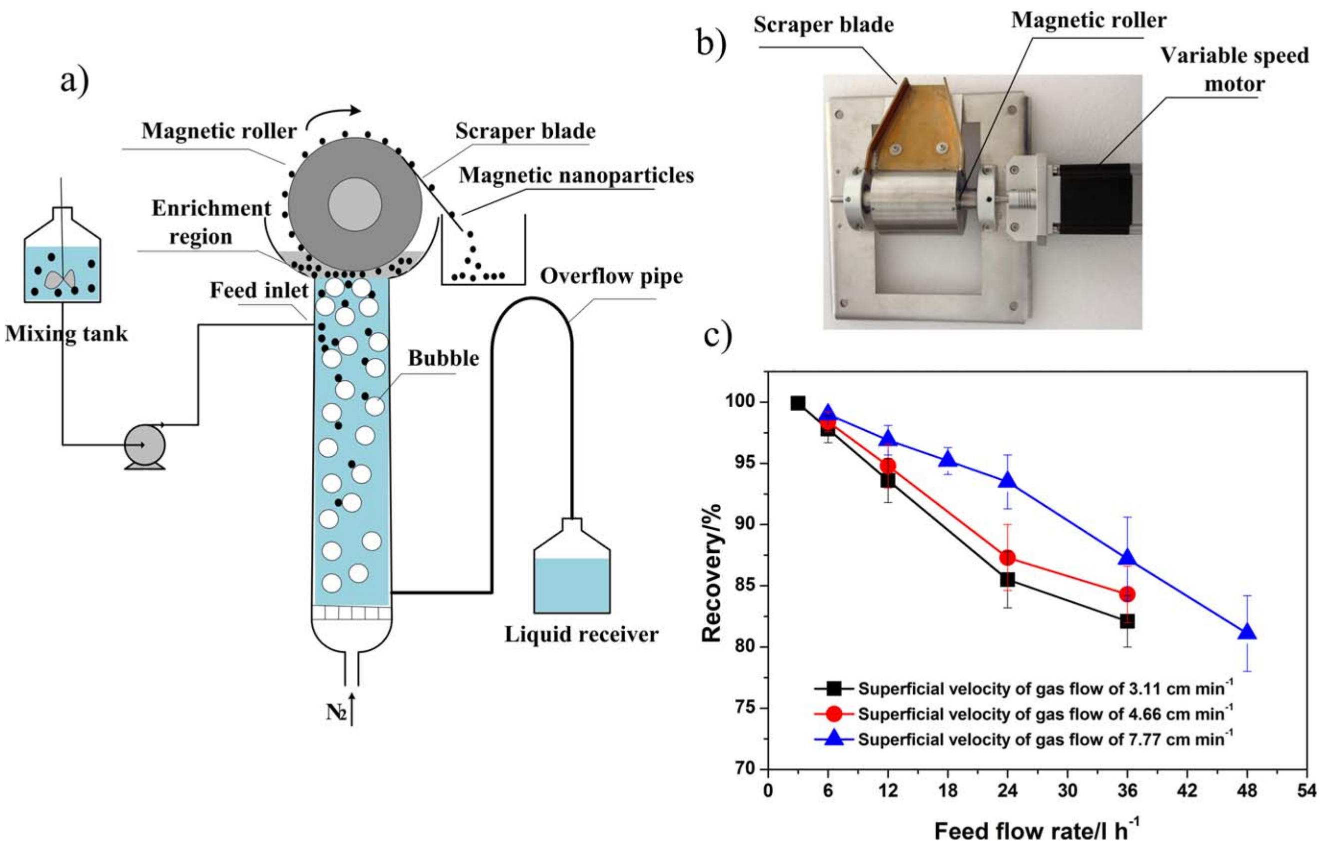

Figure 3. (a) The schematic diagram of continuous gas-assisted magnetic separator. (b) The picture of key component in gas-assisted magnetic separator. (c) Gas-assisted magnetic separator for continuous recovery of BSA-loaded CMNs from dilute solution, experiment conditions: CMNs concentration, 0.5 mg mL^{-1}; pH, 4.8 (0.02 M acetate buffer); BSA amount on CMNs, 149.2 mg g^{-1}; the speed of magnetic roller, 18 rpm.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

CMNs from dilute solution. In biotechnology, large-scale and continuous recovery of magnetic microspheres with strong magnetic response from dilute biosuspension remains an important and intractable problem, let alone magnetic nanoparticles with weak response. The widely accepted HGMS is generally used for routine laboratory scale in a batch mode. Due to the dramatically increasing costs for device and operation with the scale-up of HGMS, few attempts to scale-up this separator have been reported for recovery of magnetic microspheres, and there is no report for scalable recovery of magnetic nanoparticles thus far.[2,18]

The results of continuous recovery in Figure 3c show that the throughput in our separator increases with increasing gas flow rate and reach 18 L h^{-1} with the recovery of more than 95% at superficial velocity of gas flow of 7.77 cm min^{-1}. The developed separator can be easily operated in a batch mode, also. For batch of 2.5 L of the same feed solution, the separation time with the recovery of 96.2% is only 1.8 min at superficial velocity of gas flow of 7.77 cm min^{-1}. These results suggest that large-scale recovery of magnetic nanoparticles with high efficiency can be continuously or intermittently achieved in the gas-assisted magnetic separator.

Furthermore, the designed separator is easily scalable and low-cost. First, easy scale-up can be obtained in a continuous or batch mode. Intermittently, larger scale separation in a certain range can be carried out by increasing the height or the diameter of the flotation column due to no limit of the capture distance in this separator. It is interesting that larger scale recovery possibly has the higher separation efficiency due to the increasing separation rate with the increasing height of the column (shown in Figure 1c). Continuously, larger scale recovery can be simply achieved by increasing gas flow rate (shown in Figure 3c) and the capture efficiency of bubbles on particles (such as the increase of column diameter, the decrease of bubble sizes, and so on). More importantly, it is expected that the use of higher field and higher gradient with the scale-up of this separator is not required to make up for the decreasing magnetic force with the increasing distance. Furthermore, the concentration effect of bubbles on particles solution means itself the scale-up of the throughput in this separator.[13] And then, in terms of the cost, low-field permanent magnet, simple magnetic system design without the magnetic medium, and no requirement of higher magnetic field with larger scale provide this magnetic separator with low costs in device and operation.

In summary, we develop gas-assisted low-field MS method for rapid separation of magnetic nanoparticles from large volume suspensions. Low-field MS speed can be significantly improved by bubbles and the greater improvement can be further obtained by increasing gas flow rate. The limitation of magnetic force on the capture distance can be overcome by bubbles and interestingly, the speed of this remote capture increases with the increasing distance. These make low-field MS easily scalable. These effects of bubbles are practicable not only for hydrophobic nanoparticles with good flotability but also for hydrophilic ones without flotability. Based on this novel method, we develop a medium-free continuous gas-assisted magnetic separator on small pilot scale using low-field permanent magnet. This separator has continuous scale of 18 L h^{-1} and batch scale of 2.5 L in 1.8 min with good recovery for separation of BSA-loaded CMNs from dilute solution of 0.5 mg mL^{-1}, as an example of large volume suspensions in biotechnology application. Furthermore, this separator is easily scaled up, low-cost, and free from the use of higher magnetic field with larger scale. We see its great potential in the areas of MS such as biotechnology and water treatment.

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