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Review

Magnetic separations: From steel plants to biotechnology

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ABSTRACT

Magnetic separations have for decades been essential processes in diverse industries ranging from steel production to coal desulfurization. In such settings magnetic fields are used in continuous flow processes as filters to remove magnetic impurities. High gradient magnetic separation (HGMS) has found even broader use in wastewater treatment and food processing. Batch scale magnetic separations are also relevant in industry, particularly biotechnology where fixed magnetic separators are used to purify complex mixtures for protein isolation, cell separation, drug delivery, and biocatalysis. In this review, we introduce the basic concepts behind magnetic separations and summarize a few examples of its large scale application. HGMS systems and batch systems for magnetic separations have been developed largely in parallel by different communities. However, in this work we compare and contrast each approach so that investigators can approach both key areas. Finally, we discuss how new advances in magnetic materials, particularly on the nanoscale, as well as magnetic filter design offer new opportunities for industries that have challenging separation problems.

Contents

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1. Introduction and history

The properties of magnetic materials were identified as early as the sixth century BC, but the means by which magnets could move material remained only a curious phenomenon until the late 18th century (Livingston, 1997). As Gauss, Helmholtz and others developed a framework for electricity and magnetism, the reasons that magnets could move materials such as lodestone became apparent. This once mysterious force was quickly put to use in the nascent chemical and mining industries. In 1792 a patent was filed by William Fullarton describing the separation of iron minerals with a magnet and the field of magnetic separations was born (Gunther, 1909; Parker, 1977). The early applications relied on the intrinsic magnetic properties of sediments for separation. In 1852, magnetite was separated from apatite by a New York company on a conveyor belt separator (Gunther, 1909). Later, a new line of separators were introduced for separation of iron from brass fillings, turnings, metallic iron from furnace products and magnetite from plain gangue (Gunther, 1909). From these beginnings, magnetic separation technology has found its way into increasingly complex and diverse industrial processes (Fig. 1).

The basic principle behind magnetic separations is remarkably simple and remains unchanged from these early examples. It relies on the simple fact that materials with differing magnetic moments experience different forces in the presence of magnetic field gradients; thus, an externally applied field can handpick out of physically similar mixtures those components with distinctive magnetic characteristics (Svoboda and Fujita, 2003). The use of this principle is straightforward in mixtures where a magnetic component is known to exist; an intrinsically magnetic material can be separated using electrically powered electromagnets or strong permanent magnets. The process is generally binary and results in a magnetically rich retentate (usually a solid) and the residual non-magnetic solvent.

The 1950s were a time of great expansion for the field of magnetic separations as the introduction of high gradient magnetic separation (HGMS) systems permitted faster and more general magnetic separation processes (Delatour, 1973; Oberteuffer, 1973; Gerber and Birss, 1983). HGMS works through the application of large static fields (~1 T) to columns containing ferrous matrices such as steel wool; these irregular surfaces give rise to magnetic gradients as high as 10^4 T/m which generate forces large enough to capture even weakly magnetic particles in a flow stream (Kolm, 1975; Moeser et al., 2004). This new technology meant that magnetic separations could be applied more universally to separation problems where particulate matter was not strongly magnetic. The use of HGMS in water treatment, for example, provided a way to clarify water with high sediment loads, provided that the sediment has some weakly magnetic character. A larger market was found in the steel industry where HGMS separators became critical components for purifying high grade, low iron content steel.

More recently, separations using external magnetic fields have become commonplace in biotechnology where they are used for both protein purification as well as flow cytometry (Melville et al., 1975; Khng et al., 1998; Berger et al., 2001). In these contexts, separators apply relatively small field gradients (500 T/m) to fixed volumes of solution with the aim of removing a valuable biological components. Such an approach to separations is more as a 'batch process', and it works well for biomedical research laboratories where solution volumes are small and separation speed is not a major issue. However, the small scale and time consuming nature of biomagnetic separators precludes their application in biological manufacturing processes. In addition, the separators themselves are standalone configurations of permanent magnets which require little upkeep or even power. This separator simplicity is offset by the need for magnetic beads that are coated so as to bind to particular biological components (Ugelstad et al., 1983; Haukanes and Kvam, 1993; Lewin et al., 2000). As a result, the technique is not that general and conventional biomedical researchers can only use magnetic separations if a commercial magnetic bead source is available for their targets. Commercial sources for magnetic beads have grown substantially in the past decade, however, and a wide variety of proteins, cells and other biomacromolecules may be selectively removed using these methods.

1.1. Magnetic separations: their unique position among separation technologies

The problem of separating materials, whether they are specialized chemicals, high purity steel or valuable pharmaceuticals, from product streams is a near universal one for any manufacturing process. When speed is not an issue and the materials of interest are solids or flocculated products, sedimentation or centrifugation is routinely employed. For faster processing, filtration is a well established method for removing waste or concentrating product. Given these standard methods it is not always obvious that magnetic separations could or should be applied to a given problem. Certainly, if part of a mixture is intrinsically magnetic then magnetic removal is often the best solution. In these cases, magnetic separations generally offer higher throughput with greater specificity than equivalent centrifugation or filtration methods (Kolm et al., 1975; Fletcher, 1991; Hubbuch et al., 2001; Moeser et al., 2004).

However, even in the absence of intrinsically magnetic components the use of designer magnetic beads—targeted to the product of interest—can make a magnetic separation feasible for virtually any system. Such processes offer very different kinds of tradeoffs in speed and selectivity as opposed to the more conventional approaches. A consideration of the unique advantages of moving materials with external fields, as opposed to other conventional alternatives, is detailed in Table 1. For the purposes of this analysis we considered both the slower 'batch' model for magnetic separations as well as the faster flow separators based on the high gradient magnetic columns. We also limit our comments to separation processes for materials in liquids, a case which captures the majority of current application in this area.

An important feature of a magnetic separation is that the product stream meets with virtually no flow resistance as it moves through a separator; this is in stark contrast to filters which use a solid phase as the basis for the separation process. Filtration is particularly challenging when submicron particles or biomolecules are the target products; this requires filter pore sizes well under a micron (ultrafiltration) or even a submicron (nanofiltration). The flow resistance that this solid phase introduces to the system is significant, and industrial membrane filters often must operate with hundred of pounds of solution pressure (many times the flow of a fire hydrant) to maintain flow rates of several milliliters per minute. Such units require not just energy-intensive pumping stations, but also expensive and high performance fittings and valves. Filters also can become fouled with a wide variety of contaminants requiring backwashing procedures and ultimately replacement.

Conventional magnetic separators face few of these problems. In high-gradient flow systems, the columns are loosely packed with steel wools that offer virtually no resistance to flow. Reasonable operating pressures and conventional pumps are suitable for these systems, though the electromagnets that are needed for very high gradient separations do require significant energy. For separations in which speed is not an issue, then the batch magnetic separators are interesting options. Because they usually generate the fields with permanent magnets, they can operate without any external power; with the appropriate beads, such systems can remove a greater variety of substances than those accessed through sedimentation. This

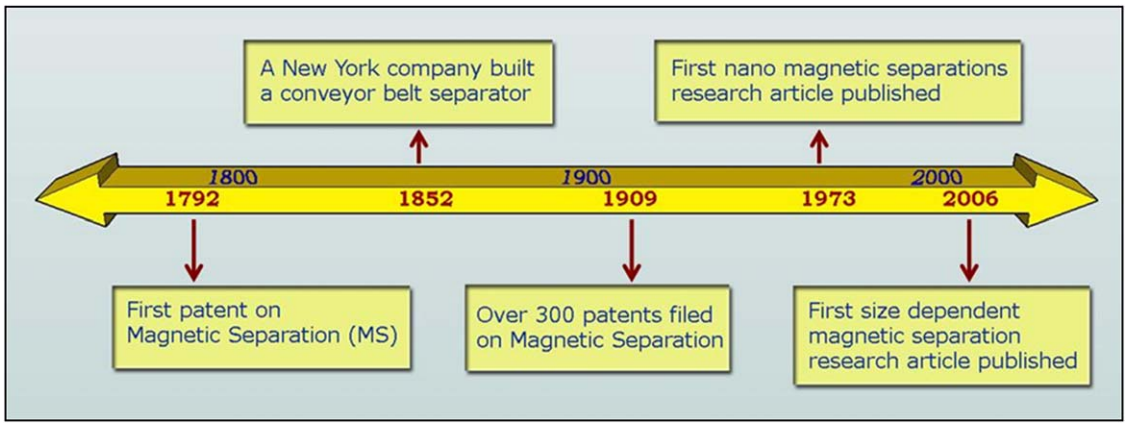

Fig. 1. The evolution of magnetic separation technology.

Table 1
Industrial applications of magnetic separations (adapted from Parker, 1977).

Application area	Objective
Chemical and related industries	Tramp metal removal from machinery to avoid wear and malfunction
Food industries	
Coal processing plants	
Metals production and recycling industries	
Raw materials processing plants, such as cement, glass, semiconductors	Removal of iron and derivatives' contamination
Mineral post processing industries	Separation and enrichment of magnetic ores (magnetite, hematite, ilminite, etc.)

makes them particularly attractive for small-volume separations in low infrastructure settings.

While magnetic separations are in principle excellent choices for many problems, their widespread application has been limited by the complexity required in separator design and bead technology. In the case of flow separations, cumbersome and expensive electromagnets are used to create external fields in excess of a Tesla; the requirement for high gradients also limits column diameters and thus reduces throughput. In the batch separations favored in biotechnology, permanent magnets in a multipole configuration provide the relatively low gradients needed and their set-up and use is easy and immediate (Hoffmann et al., 2002). The trade-off here is that these low fields produce only very small magnetic forces on particles. Since the magnetic force is proportional to the particle volume, the small field gradients are generally offset by the use of larger magnetic beads (Fletcher, 1991; Cotten and Eldredge, 2002; Moeser et al., 2004). This lowers the available surface area for biomolecular recognition and adsorption, and has precluded application of this technology to biological separations on the larger scale (Safarik and Safarikova, 2002). Our group and others are working on ways to better design nanoscale magnetic beads so as to overcome these and other limitations. This materials design process must be guided by a more quantitative and formal description of the process of magnetic separations, the topic of the next section.

2. Modeling magnetic separations

The magnetic separation process is amenable to simple modeling and such treatments date back to the 1950s; most analyses assume that the materials being removed act independently and that macroscopic models for fluid dynamics are appropriate. These constraints make it straightforward to describe the many forces acting on particles in a flow, such as the magnetic force, Brownian motion, gravitation, and friction. What results is a universal equation that relates the net force on a particle to input parameters such as the particle size, magnitude of the field gradient, frictional coefficient, and the magnetic moment of the particle. Obtaining precise values for these experimental data is difficult and limits the predictive power of these models. Still, these treatments provide an essential foundation for improving the materials and systems used for magnetic separations.

2.1. Simple treatments for magnetic separations

Magnetic separation occurs as a result of the diverse and competing forces acting on a particle during flow in the presence of an external field. These include a hydrodynamic drag force due to the flow velocity; a magnetic force due to the gradient of the applied magnetic field; gravitational forces for large and dense particles; and finally a diffusive force which, arises from the intrinsic Brownian motion of particles. While the first three are deterministic forces that control a particle's trajectory, the latter is a randomizing force that must be exceeded if an ensemble of particles is to experience net movement during some time interval. Put in other terms, if the energy available to move a particle does not exceed its thermal energy due to Brownian motion then it is not possible to set up a concentration gradient (Fletcher, 1991).

Perhaps the most important factor to include in models of magnetic separations is the role of inter-particle forces such as Helmhotz double layer interaction, dipole–dipole interaction and Van Der Waals attraction. Thus, the magnetic, dipole–dipole interaction and Van Der Waals forces aid the process of separation, whereas, diffusion, double layer interaction and drag force act against the separation. Also, the particles are found to reversibly aggregate in presence of high field gradients, which would increase the net magnetic moment to a magnitude much stronger than the competing forces (Yavuz et al., 2006a,b).

3. Magnetic separations use in column formats: examples

Magnetic separators used on the industrial scale are overwhelmingly high gradient systems which function as a column in continuous flow operations. The speed and efficiency of these systems

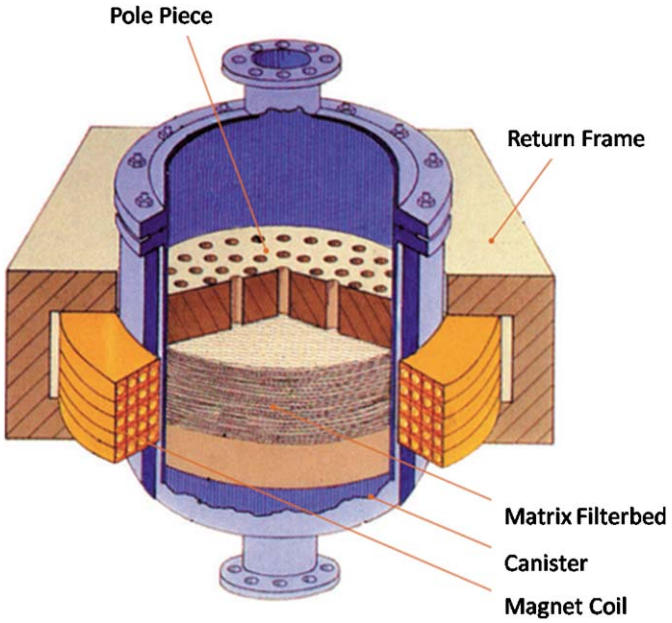

Fig. 2. Metso® high gradient magnetic separators (HGMS) are designed to recover weakly magnetic material from non-magnetic matter and can be used for many applications including the processing of clays, iron ores, rare earths and industrial minerals. In addition to the strongly magnetic minerals of Fe, Co, and Ni, a vast number of weakly magnetic minerals, which are not normally treatable by ordinary magnetic separators, may be processed by high gradient magnetic separators. Metso HGMS separators are able to remove even weakly paramagnetic materials (from Metso minerals).

have been exploited for decades and the early stages of the industry were marked by notable optimism: "Virtually every process in the chemical engineering industry is a potential application (for HGMS). Many previously unthinkable processes will now become practical, and many previously practical ones will become unthinkable. It has already happened in the kaolin industry, and is beginning to happen elsewhere." (Henry Kolm, September 1975) (Kolm, 1975). While these systems are not as ubiquitous now as their inventors anticipated thirty years ago, their applications have expanded notably.

3.1. Kaolin (clay) decolorization

Kaolin (a.k.a. china clay) is a clay mixture primarily consisting of kaolinite ($Al_2O_2SiO_2.2H_2O$ or $Al_2Si_2O_5(OH)_4$) mineral (Gerber and Birss, 1983). It is named from the Kaoling Hills of the city of Ching-te chen where fine Chinese porcelains were produced; its resistance to acids and alkalis alike was greatly prized. Today, however, it's mostly used in the paper manufacturing industry where it plays dual role, as a filler between the pulp fibers and as a surface coating for a white glossy finish (Saikia et al., 2003; Iannicelli and Pechin, 2000; Gerber and Birss, 1983, China Clay Producers Association)

Natural kaolin has color as mined due to the iron containing micas, tourmaline, pyrite, anatase and rutile present in the material. To remove these impurities, kaolin can be magnetically cleaned with a continuous high gradient magnetic separator to produce highly white material suitable for paper or porcelain (Oder and Price, 1973; Oder, 1976; Lofthouse, 1981; Gerber and Birss, 1983) (Fig. 2). Fig. 3 shows kaolin mineral before and after the decolorization process. Because of the resistance of kaolin impurities to other chemical cleaning methods, HGMS handles 75% of the world production of white porcelain and paper (Oder, 1976). A typical plant would have an HGMS with a filter diameter of about 2 m and capacity up to 20 t/h (Hirschbein et al., 1982).

3.2. Steel factories and power plants

On average, generating 1 t of steel requires 151 t of water for cooling and cleaning purposes; the resulting wastewater is filled with many magnetic particulates and other iron-containing impurities (Table 1). Those particles, especially when present in gas and hot water streams, cause significant problems in processing and must be removed. Conventional methods for cleaning steel mill waste and process waters include sedimentation, flocculation followed by sedimentation, and fixed bed filtration. Such approaches require either large areas for settling tanks and clarifiers or expensive and short-lived filter systems (Oberteuffer et al., 1975). Magnetic separation has emerged as an ideal solution for this industry, and it has offered great time, space and cost savings (Oberteuffer et al., 1975; Harland et al., 1976; Gerber and Birss, 1983). In a sample treatment at Kawasaki Steel Corporation of Japan, a 3 kOe field strength, 2.1 m diameter magnetic filter removes 80% of contaminants from the cooling wastewater of vacuum degassing process (Hirschbein et al., 1982). Similar use in treatment of wastewater can also be found in power plants (both conventional and nuclear). For these cases, HGMS is used to remove ferromagnetic or paramagnetic particulates which extends the lifetime of cooling systems (Gerber and Birss, 1983).

Magnetic separations can also be used to treat pollution. Fly ash from coal power plants is 18% iron oxide. Magnetic filtration has been applied to capture 15% of waste fly ash, thus providing a means for recycling. Estimates show that this can replace some of the magnetite used in industry (Hirschbein et al., 1982). Fig. 4 shows an example of a ball mill separator used in these operations.

3.3. Enrichment of ores–mineral beneficiation

The treatment of ores with magnetic separation is carried out primarily to enrich iron-containing ores. Conventional chemical and settling methods are not suited for this purpose given the similar density and reactivity of transition metal minerals. The magnetic nature of iron species, however, is unique and thus a natural target for magnetic separations. Among the iron ores taconite is most often subjected to magnetic treatments. From a taconite ore (33% iron) Kelland (1973) was able to recover iron at 95% on a 5 cm/s flow rate. Today, Metso Minerals, Inc. (formerly Sala International AB) offers magnetic separators that can separate iron from ores with nearly 100% efficiency (depending on the particulate sizes, magnetic field and flow rate). Fig. 5 shows a successful continuous HGMS separator used for these purposes.

Magnetic separation of pyrite (FeS_2) from coal for desulfurization is also a common process (Maxwell and Kelland, 1978). The weakly magnetic nature of pyrite, however, requires that the raw ore be pre-treated thermally to convert the pyrite (FeS_2, $M_s = 0.3$ emu/g) to more strongly magnetic pyrrhotite (Fe_7S_8, $M_s = 22$ emu/g). Up to 91% removal of sulfur from coal can be achieved by microwave heating followed by a magnetic separation (Uslu et al., 2003). Fig. 6 shows an industrial scale drum separator used in large scale applications for powders such as coal.

3.4. Food industry

Strict food quality standards require the food products to be contaminant free, where mainly rare earth elements (REEs) constitute the majority. The food industry, therefore, has found magnetic separations to be an ideal method to remove REEs from food ingredients. Similar to the ore beneficiation or desulfurization, the target substances are weakly magnetic and require the high gradients of a magnetic field to be removed in a continuous food production line. Bunting Magnetics Co. offers magnetic metal separators and metal detectors for the quality of food and extended service life of

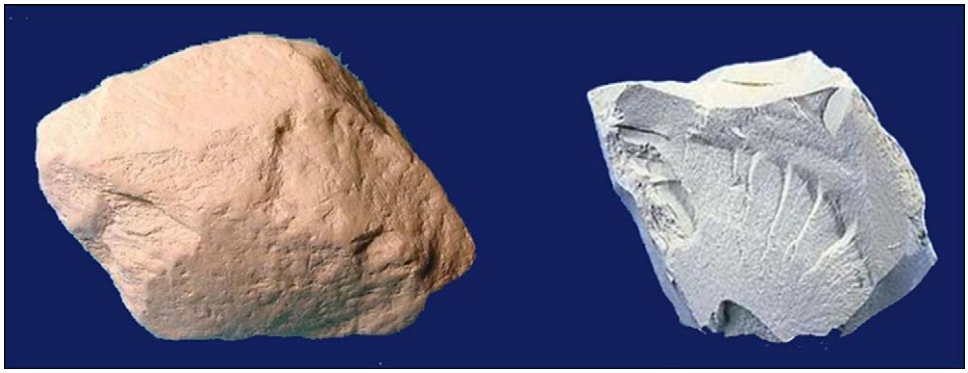

Fig. 3. Kaolin decolorizes to white after magnetic separation (adapted from R. Weller/Cochise College and US Geological Survey's mineral collections).

Fig. 4. A ball mill separator from Eriez. Separation of ball mill grinding ball segments from the discharge. From Eriez Magnetics, Inc.

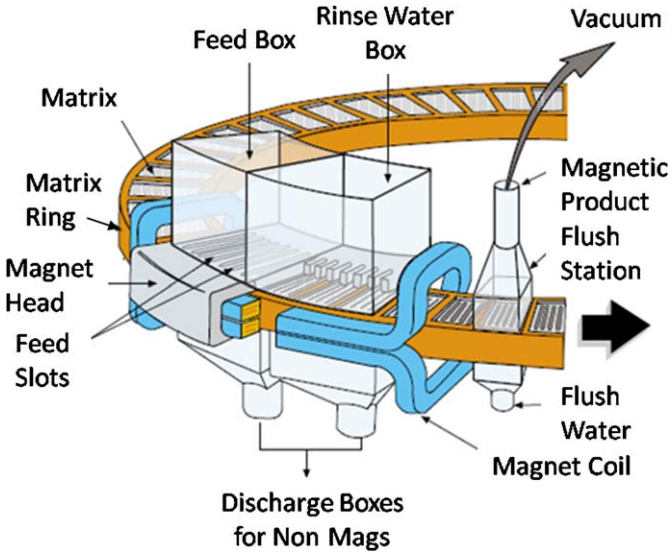

Fig. 5. Continuous high gradient magnetic separation for many low susceptibility minerals that are associated with other minerals or have extra Fe in the crystals, and are hence often possible to separate (from Metso minerals).

the processing equipment, especially for cheese processing, chocolate plants, pet food processing, flour mills, spice plants, vegetable processing. Removal of both ferrous and nonferrous tramp metals is achieved by their line of food safety products for the food processing industry. Fig. 7 shows case studies from Greenwood Magnetics Ltd., another company that produces magnets and assembly systems for cleaning REEs off of the food production lines.

3.5. Water treatment and metal removal

With the new, lowered maximum permissible concentration for arsenic in drinking water (10 μg/l), effective since January 2006 (Arsenic Rule, 2006), techniques for better arsenic remediation without much desorption have gained more importance. Currently, coprecipitation, adsorption in fixed-bed filters, membrane filtration, anion exchange, electrocoagulation, and reverse osmosis are of methods of interest (Twidwell et al., 1999), however, cost efficiency and waste quantity (Hossain et al., 2005) requires further development that would aid in resolving the problem (see Table 2).

Arsenic adsorption and desorption are heavily influenced by adsorbent particle size (Yean et al., 2005; Mayo et al., 2007). Nanoscale magnetite (Fe_3O_4, 12 nm) can remove 200 times better than its commercial counterparts (Table 3), which allows a significant cut in waste, instead of 1.4 kg of bulk iron oxide to remove arsenic (500 μg/l) from 50 l of solution, 15 g of nano magnetite can be used (Yavuz et al., 2006a,b). Apart from surface area increment, an obvious gain while going down to nanoscale, available open sites with the proper chemistry (free Fe on the surface) can be accounted for this unexpected result. Size dependent magnetic properties bring controllability and along with mobility, a critical nanoscale advantage, provides unique applicability, if put in a system, in especially household uses where electricity is not readily available.

As early as 1970s Delatour (1973) and Delatour and Kolm (1975) treated water samples from the Charles River (Fe_3O_4 seeding, 5 ppm Al^{3+}) with a high flow velocity HGMS ($V_0 = 136$ mm/s, $H_0 = 1$ T) and reduced coliform bacteria from 2.2×10^5/l to 350/l, turbidity by 75%, color by 95%, and suspended solids by 78% (Gerber and Birss, 1983). Later, Bitton and Mitchell removed 95% of the viruses from water by magnetic filtration following a 10 min of contact period with magnetite (added to be 250 ppm) (Gerber and Birss, 1983). The following years, Boliden Kemi AB reduced phosphorus of water supplies at least 87% (Gerber and Birss, 1983). Also known as Sirofloc process, micron-sized magnetite is also used to remove color, turbidity, iron, and aluminum from water sources as an alternative to metal-ion coagulation (Gregory et al., 1988). Recently, Denizli, and coworkers magnetically modified yeast cells for facile capture of mercury with fast biosorption rates (within 60 min) and efficiency (76.2 mg/g for Hg^{2+}) (Yavuz et al., 2006a,b).

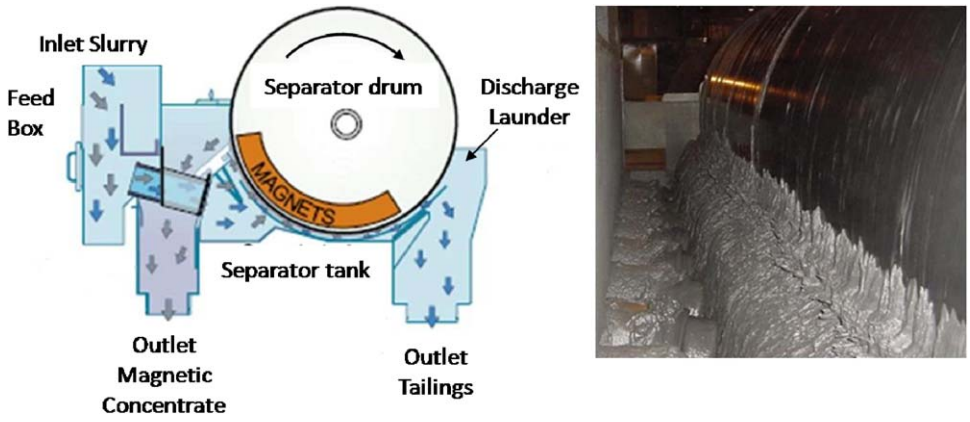

Fig. 6. An industrial scale drum separator used in large scale applications. From Eriez Magnetics, Inc.

Fig. 7. (Left) A single row easy-clean grid box which contains high-density rare earth easy-clean magnetic tubes filters loose tea with a flow rate of 5 tph. (Middle) A water-jacketed pipeline magnet was manufactured to suit a 4 in pipeline pressure resistant up to 10 bar, nine high intensity rare earth magnets (11 500 G) filter liquid chocolate flowing at 300 l/min. The pressurized heated water-jacket maintains the temperature of the chocolate. (Right) The Bullet magnet that is used by a flour producer in which flour flows upwards through the 5 in pipe and any ferrous contamination is removed by the high intensity rare earth bullet magnet (8500 G min).

Table 2
Sources of contaminants in a steel production process (adapted from Oberteuffer et al., 1975).

Source of contaminant	Contaminants
Coke production	Non-magnetic particles, organics, and oils
Iron manufacturing	Magnetic particles and organics
Steel production	Magnetic particles
Hot formation	Magnetic particles, oils, and acids
Cold finishing	Magnetic particles and oils

Table 3
Arsenic removal by nano-sized magnetite.

Particle size (nm)	As (V) or As (III)	Residual as concentration (μg/l)	% Removal
12	As (III)	3.9	99.2
20	As (III)	45.3	90.9
300	As (III)	375.7	24.9
12	As (V)	7.8	98.4
20	As (V)	17.3	96.5
300	As (V)	354.1	29.2

A comparison of As removal efficiency, assuming a treatment of 2 l of As solution (500 μg/l) with 1 g Fe_3O_4 (Yavuz et al., 2006a,b).

4. Biotechnological (batch) applications

The ability to control remotely inspired many biotechnologists and medical scientists to investigate magnetic solutions for several biochemical processes, such as protein and cell separations and purifications, magnetic drug targeting and delivery, and enzyme-based biocatalysis. Unlike industrial applications, in-lab or batch applications require tailor-made magnetic materials but remain fine with steady, not continuous, bench-top or batch, process solutions. First, we will give key components of a magnetic material to be used in vivo and then review some of the biological applications of magnetic separation.

4.1. General principle of use

In vivo applications of magnetic materials require biocompatibility. Thus, biochemists tend to use naturally existing minerals, such as magnetic iron oxides (magnetite, Fe_3O_4 and maghemite, γ-Fe_2O_3), due to their biologically safe nature i.e. in the ferrofluids (Tartaj et al., 2003). Key requirements for a bio-magnetic separation material are biocompatibility, suitable linkers, functional layers on magnetic core, protective layer, antigen detection, shape recognition, fluorescent signaling (Fig. 8).

4.2. Protein and DNA purification

Magnetic separation of biological entities had proven to be a rapid and effective process for over 30 years (Robinson et al., 1973; Dunnill and Lilly, 1974; Guesdon and Avrameas, 1977; Hirschbein and Whitesides, 1982; Hubbuch et al., 2001). Proper coating and

labeling of the magnetic particles and the target species provides simple and fast purifications with reduced costs (Setchell, 1985; Safarik and Safarikova, 2004). Although very effective, magnetic affinity separations need to be very specific. Immobilization of ligands on the magnetic adsorbents for the capture of the target species is crucial; this is perhaps one reason that conventional liquid column chromatography remains the gold standard for demanding purification processes (Safarik and Safarikova, 2004). Recent studies on magnetic materials for protein separations relied on silica coated magnetite with amino functionality for salmon sperm DNA elution (Bruce and Sen, 2005), phospholipid coated magnetite for myoglobin recovery (Bucak et al., 2003), polyethylenimine coated magnetite for purification of plasmid DNA from bacterial cells (Chiang et al., 2005), magnetic separation of erbium (III) attached anionic biomolecules and particulates (Evans and Tew, 1981), magnetic polyacrylamide–agarose beads for measuring rabbit antibody (Guesdon and Avrameas, 1977), magnetic polymer latexes for isolation of trypsin from pancreatic extract (Khng et al., 1998), ProtA-immobilized magnetic immunomicrospheres for immunoaffinity purification of antibodies IgG2a from mouse ascites (Liu et al., 2004), silica coated magnetite with iminodiacetic acid functionality for bovine hemoglobin (BHb) and bovine serum albumin (BSA) (Ma et al., 2006), streptavidin-functionalized magnetic nanoparticles for biotinylated horseradish peroxidase (Mertz et al., 2005), Nickel–NiO–BSA–chymotrypsin for casein hydrolysis (Munro et al., 1981), magnetic affinity support for adsorption of lysozyme (Tong et al., 2001), streptavidin–biotin coated magnetic beads for DNA–RNA isolation (Uhlen, 1989), polyethyleneimine coated magnetite for virus capture (Veyret et al., 2005), carboxyl-modified magnetic nanobeads for the isolation of genomic DNA from human whole blood (Xie et al., 2004), TeNT-linked iron oxide nanobeads with dextran coating for explaining the relative capacity of the specific compartments of a cell resulting from endocytosis through different receptors that promote antigen presentation and immune (Perrin-Cocon et al., 2001). Fig. 9 illustrates the standard setup for a bench-top magnetic separation (Tartaj et al., 2003). Fig. 10 shows a summary of the available magnetic separators (Safarik and Safarikova, 2004).

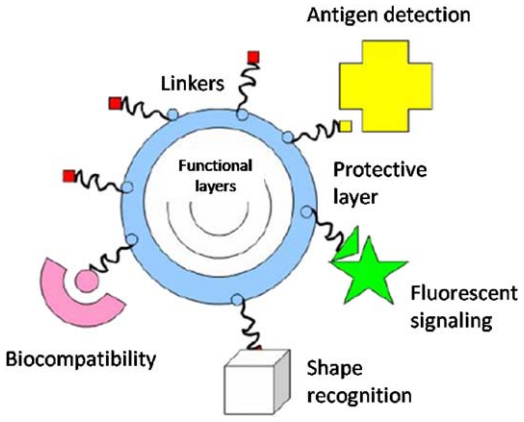

Fig. 8. On a single particle, several necessary sections of a magnetic material that could be used in biological systems is summarized (reprinted with permission from Salata, 2004).

In an excellent review, Safarik and Safarikova discuss advantages and the equipment for a successful protein purification via magnetic means with a full scan of magnetic separation applications in isolation of enzymes, antibodies, and other proteins (Safarik and Safarikova, 2004). The efforts for the industrial scale applications are noteworthy and can be applied for a few biological molecules (Safarik et al., 2001, 2007; Hubbuch and Thomas, 2002). Magnetic separation-based protein analysis and detection systems on chips are of great interest for early diagnosis for fatal infections. Bio-barcoded magnetic beads (Nam et al., 2003), microfluidic biochemical detection system (Choi et al., 2002), micromachined magnetic particle separator (Ahn et al., 1996) are prominent examples of this field. Recently, nanorods of Ni with Au edges were successfully used to remove His-tagged proteins with 90% recovery (Lee et al., 2004).

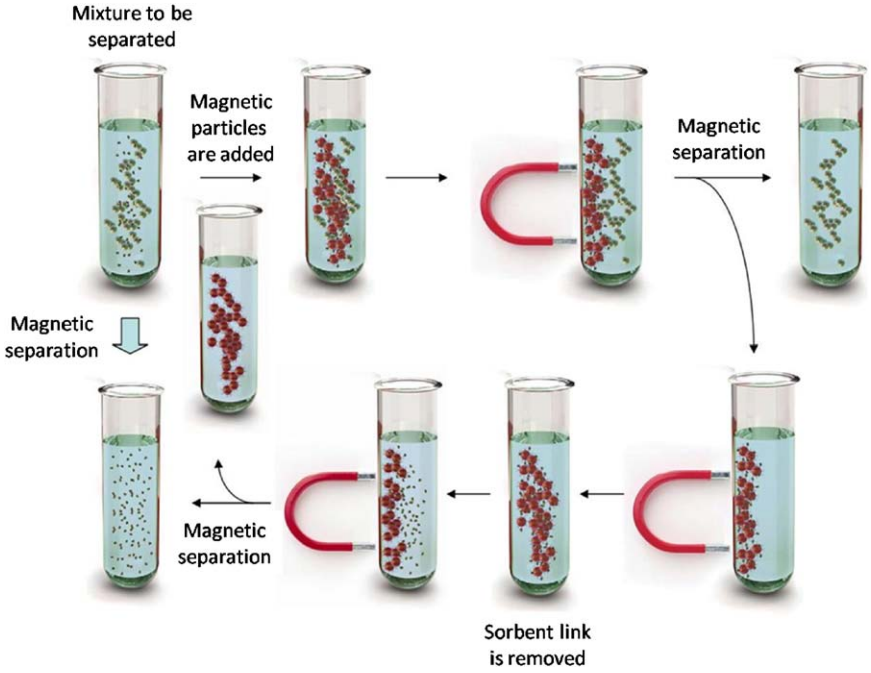

Fig. 9. A simple, standard representation of a bio-magnetic batch separation. Red particles represent magnetic nanocrystals suitably functionalized for the desired species. Gray and spherical substances are the undesired species and the conical ones are the desired ones.

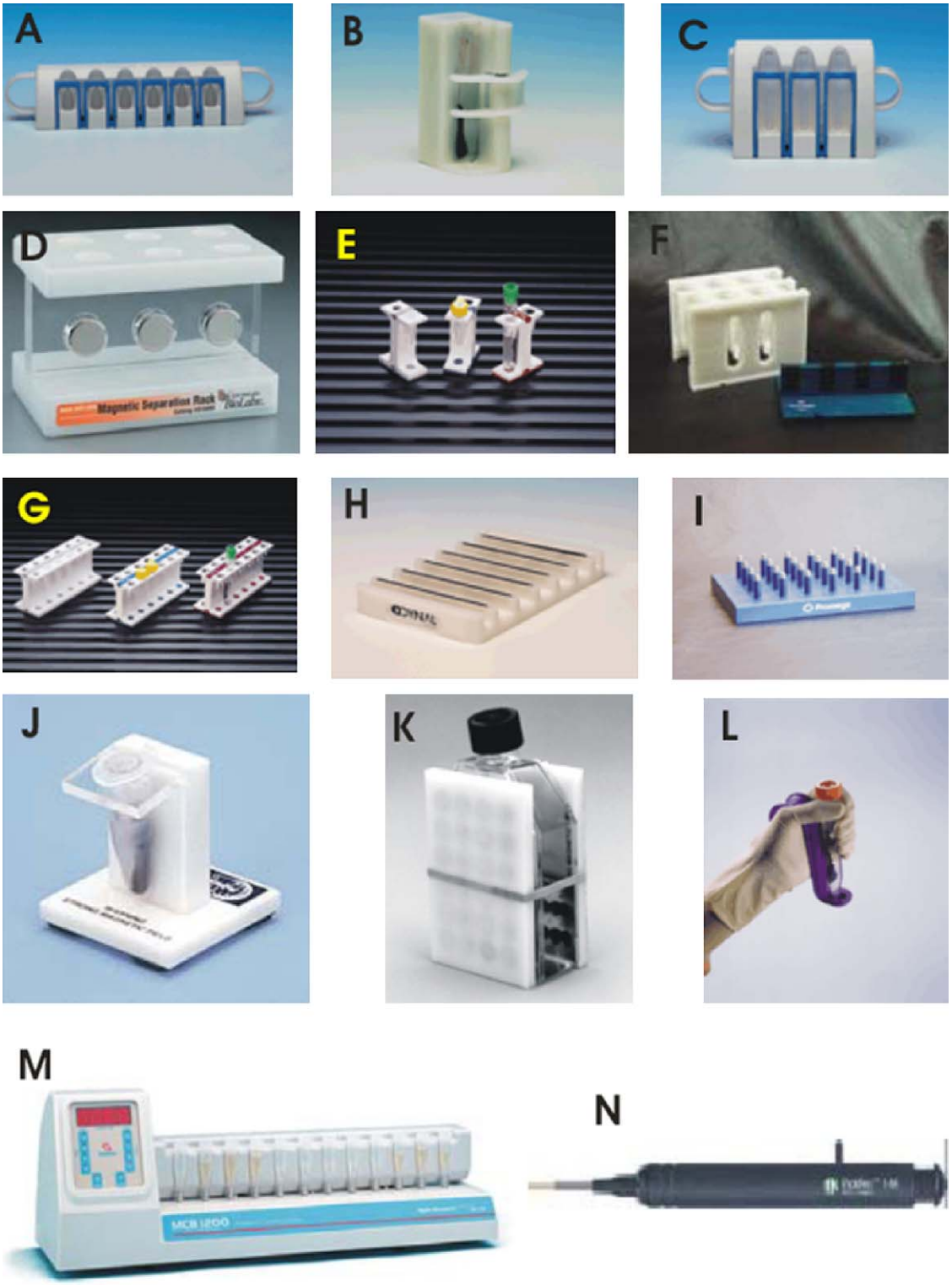

Fig. 10. Examples of batch magnetic separators applicable for magnetic separation of proteins and peptides: (A) Dynal MPC—S for six microtubes (Dynal, Norway); (B) Dynal MPC—1 for one test tube (Dynal, Norway); (C) Dynal MPC—L for six test tubes (Dynal, Norway); (D) magnetic separator for six Eppendorf tubes (New England BioLabs, USA); (E) MagneSphere technology magnetic separation stand, two position (Promega, USA); (F) MagnaBot large volume magnetic separation device (Promega, USA); (G) MagneSphere technology magnetic separation stand, 12-position (Promega, USA); (H) Dynal MPC—96 S for 96-well microtitre plates (Dynal, Norway); (I) MagnaBot 96 magnetic separation device for 96-well microtitre plates (Promega, USA); (J) BioMag solo-sep microcentrifuge tube separator (Polysciences, USA); (K) BioMag flask separator (Polysciences, USA); (L) MagneSil magnetic separation unit (Promega, USA); (M) MCB 1200 processing system for 12 microtubes based on MixSep process (Sigris Research, USA); and (N) PickPen magnetic tool (Bio-Nobile, Finland) (reprinted with permission from Safarik and Safarikova, 2004).

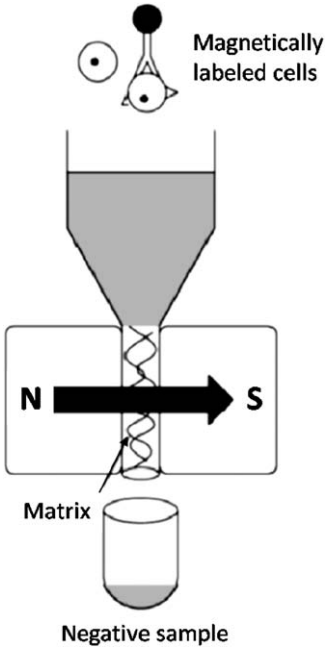

Fig. 11. Magnetically labeled cells can be separated on a gravity feed through a high gradient magnetic separator (HGMS) (reprinted with permission from Berger et al., 2001).

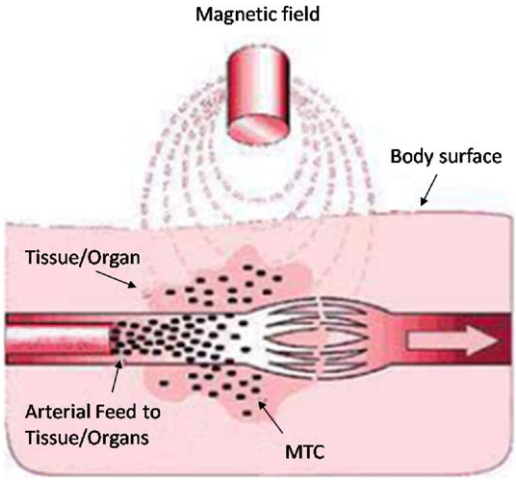

Fig. 12. Magnetic Targeted Carriers (MTC) offer a target oriented drug delivery (reprinted with permission from Saiyed et al., 2003).

4.3. Cell separation

Similar to protein purifications, magnetic separations offer rapid quantification, high cell recovery when compared to the conventional methods, i.e. centrifugation (Chang et al., 2005). As early as 1977, 99% recovery of neuroblasioma cells was obtained in a matter of minutes (Kronick et al., 1978). The same year, magnetic separation of red blood cells and lymphoid cells were also introduced (Molday et al., 1977). Magnetic separation of cells is advantageous over the conventional methods mainly because it lets target cells to be isolated directly from the medium, i.e. blood, bone marrow, tissue homogenates, stool, cultivation, media, food, water, soil etc. (Melville et al., 1975; Safarik and Safarikova, 1999).

Labeled cells, i.e. neural progenitor cells (Lewin et al., 2000), red blood cells (Haukanes and Kvam, 1993; Seesod et al., 1997; Takayasu et al., 2000; Zborowski et al., 2003), tumor cells (Wang et al., 2004), malarial parasites (Paul et al., 1981), baker's yeast (Azevedo et al., 2003), can be targeted to magnetic beads which can therefore be separated (Pankhurst et al., 2003). Magnetic moment or giant magnetoresistance of the magnetic particle-cell assembly can tell us about the location and even the count of the cells that are present (Pankhurst et al., 2003).

With efforts to take magnetic cell separation to industrial level, Berger and coworkers were able to develop a micro cell separator (Berger et al., 2001), Haik introduced a magnetic device for continuous separation of red blood cells (Haik et al., 1999) and Zborowski applied a magnetic quadrupole flow sorter on a model cell system of human peripheral lymphocytes targeted with commercial monoclonal antibodies and iron-dextran colloid (Zborowski et al., 1999). Fig. 11 shows an example of magnetic devices for cell separations. Recently, magnetic nanowires were experimented with cell separation techniques and found to be four times better in purity (80%) and recovery (85%) yields (Hultgren et al., 2004).

4.4. Drug delivery

Bio-distribution of pharmaceuticals always faces a big challenge: Unspecific, evenly distribution of the drugs all over the body. This requires a large amount of the dose to get enough of it to the target which also brings a side effect of the non-specific toxicity in healthy sectors. Among other drug targeting methods, magnetic targeting offers one of the most viable solutions to the targeting problem (Torchilin, 2000). To our knowledge, first applications in magnetic drug targeting date back to late 1970s (Senyei et al., 1978; Widder et al., 1978; Mosbach and Schroder, 1979).

For a successful delivery, a carrier must also be fully controllable. Aggregation, clogging or intrinsic, permanent magnetic behavior is completely unacceptable. Superparamagnetic iron oxides, therefore, offer both requirements for being an excellent shuttle for a successful drug delivery. Fig. 12 explains how a magnetically targeted carrier would work. Researchers at FeRx Inc. were able to craft iron particles with activated carbon (1–2 μm) and attach Doxorubicin, an anticancer drug (Wilson et al., 2004). They used the magnetic particle—drug assembly to cure cancer tumor in a reversible drug release fashion (Saiyed et al., 2003). Sadly however, FeRx, Inc. is now out of business and laid off most of its employees because of their failure in phase II clinical trials.

As can be clearly seen in FeRx example, physical (magnetic properties to drug binding capacity) and physiological (target position to body weight) limitations for the in vivo studies resulted in unsuccessful medical therapies but also encouraged more in depth research (Dobson, 2006). For this reason, using epirubicin, an anticancer drug, Lubbe and coworkers identified the potential of ferrofluids (Lubbe et al., 1999). More theoretical studies followed: a mathematical model for magnetic targeted drug delivery (Grief and Richardson, 2005), a hypothetical magnetic drug targeting system using FEMLAB simulations with the HGMS principles (Ritter et al., 2004), a two-step targeted drug delivery system (Rosengart et al., 2005), and a new method for locally targeted drug delivery with magnetic implants in the cardiovascular system (Yellen et al., 2005) were developed. Regardless, anticancer drug delivery via magnetic carriers increases drug concentration at the tumor site and limits the systemic drug concentration, by which it enhances the drug activity to multiples of magnitude (Neuberger et al., 2005).

Recent treatments with magnetic drug targeting involved using of magnetic targeted carriers (MTCs) in liver and lung (Goodwin et al., 1999), treatment of squamous cell carcinoma in rabbits with ferrofluids (FFs) bound to mitoxantrone (FF-MTX) that was concentrated with a magnetic field (Alexiou et al., 2000, 2005a,b), preparation of magnetic liposomes containing submicron-sized ferromagnetic particles encapsulating the muscle relaxant drugs,

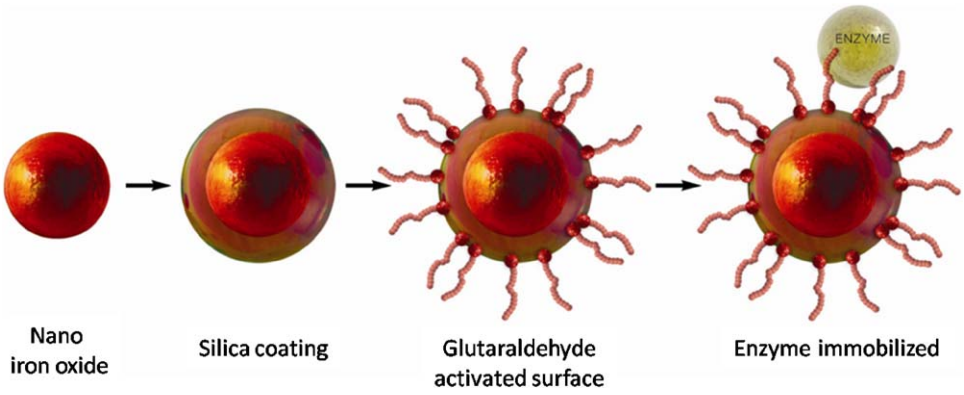

Fig. 13. Preparation of enzyme immobilized, silica coated nano iron oxide (adapted from Gao et al., 2003).

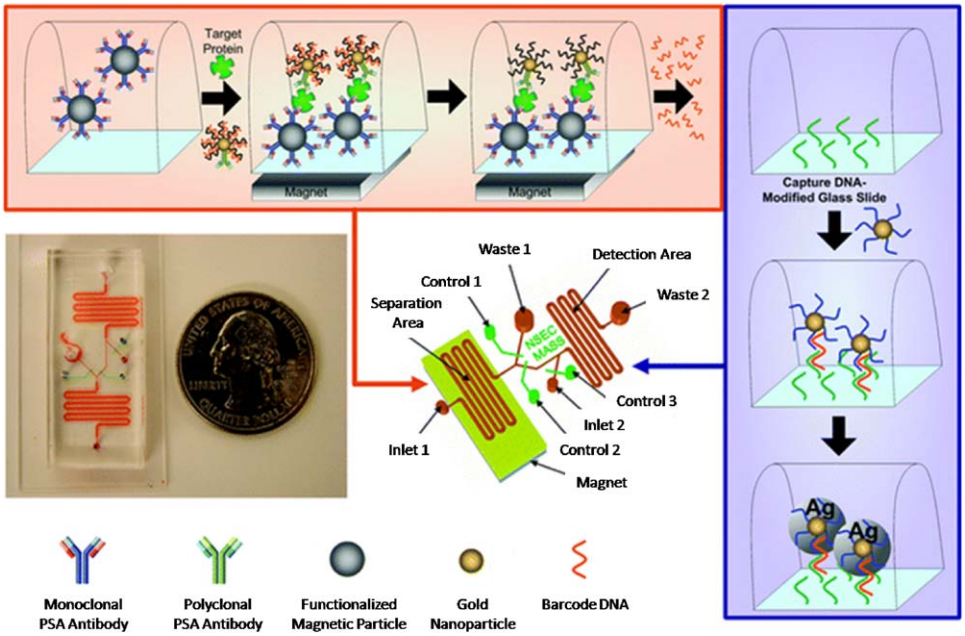

Fig. 14. Implementation of the bio-barcode assay within a microfluidic device. First, magnetic particles functionalized with monoclonal PSA antibodies are introduced into the separation area of the chip. The particles are then immobilized by placing a permanent magnet under the chip, followed by introduction of the sample and gold nanoparticles that are decorated with both polyclonal antibodies and barcode DNA. The barcode DNA is then released from the gold nanoparticles and is transported to the detection area of the chip. The detection area of the chip is patterned with capture DNA. Salt and a second set of gold nanoparticles functionalized with complementary barcode DNA sequences are introduced into the detection area to allow hybridization. Finally, the signal from the gold nanoparticles is amplified using silver stain (reprinted with permission from Goluch et al., 2006).

diadony or diperony, for local anesthesia (Kuznetsov et al., 2001), an improved method for the physical delivery of rAAV vectors *in vivo* in which virion particles are conjugated to microsphere supports (Mah et al., 2002), thrombosis treatment using a composition of ferrofluid with fibrinolytic enzyme (Rusetski and Ruuge, 1990), and nucleic acid delivery with magnetically labeled non-viral vectors (Schillinger et al., 2005).

4.5. Biocatalysis and diagnostics

Biocatalysis is a newly developing field that has much to gain from the use of magnetic separations. For this area, magnetic beads are used to immobilize biocatalysts, such as β-lactamase (Gao et al., 2003) and peroxidase (Yang et al., 2004), to permit the materials to be homogeneously dispersed and recovered after use. Fig. 13 shows how an enzyme can be immobilized on a nano iron oxide.

Diagnostics is becoming increasingly vital for especially fatal and infectious diseases such as AIDS. Yager et al. developed microfluidic diagnostic technologies to replace highly sophisticated technologies which are specifically designed for climate controlled facilities with constant supply of calibrators and chemicals, stable electricity, adequate and rapid transportation and highly trained personnel (Yager et al., 2006). A bio-barcode assay within a microfluidic device was designed to carry out diagnostics of proteins at the attomolar sensitivity enabling early detection and improved treatment at the early stages of the epidemic (Goluch et al., 2006) (Fig. 14). Ferrofluid modified trypsin was also shown to be useful in detection and quantitative determination of selected xenobiotics (Safarik et al., 2002).

5. Conclusions, further directions, and challenges

Magnetic separations on the industrial scale is a well studied and well developed area; recent research applications based on the

same principles have made these tools relevant for biotechnology. In these cases, bench top magnetic devices can be used to purify solutions in batch processing. With proper magnetic carriers that features high quality nanocrystals, with greater surface areas and more responsive magnetic cores, we anticipate an expansion of the magnetic separations in biotechnology.

The field faces many opportunities for growth in the 21st century. For industrial scale applications, the magnetic strength of separator columns can permit more rapid and universal applications. Superconducting electromagnets are already in use but designing less expensive permanent magnets that could generate massive magnetic fields would be a key factor for further development. Batch applications, which by nature are highly specific, have the ongoing challenge of designing custom magnetic beads tailor made to recognize elements of interest. For every biological species that is desired to be separated, a different antibody or binding functionalization may be required. An improvement in more universal and magnetically responsive materials would be a breakthrough. For both industrial and batch scale systems, there is an ongoing need to lower the field strengths needed to move materials in liquids, as well as create simpler and more versatile systems.

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