New classes of selective separations exploiting magnetic adsorbents

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Summary

Magnetic adsorbents enable alternative process modes of selective separations, such as the use of batch or continuous stirred-tank reactors followed by magnetic separators but also more sophisticated systems such as magnetic extractors or so-called magnetically stabilized fluidized beds. In small scale, the use of magnetic adsorbents for clinical diagnostics and bioanalytical assays is common practice and well established; however, despite several decades of research and pilot-scale campaigns, there are only few industrial applications of magnetic adsorbents. Therefore, we highlight recent equipment and process developments having the potential to overcome limitations regarding continuous operation, processable particle sizes, and cleanability. Afterward, we review the state of the art of selective separations exploiting magnetic adsorbents in the most promising fields of application, such as algae harvesting, phosphate recycling, and protein purification.

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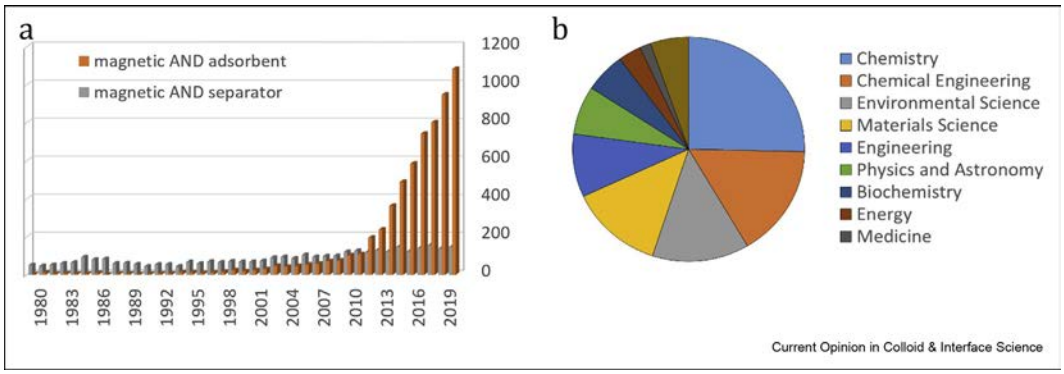
Introduction

Magnetic adsorbents are a special class of adsorbent particles, which combine a selective adsorption affinity for a certain target substance with magnetic properties, facilitating the mechanical separation, deflection, mixing, etc. of the adsorbent. Within the last decades, magnetic adsorbents have attained an almost exponentially increasing attention, resulting in more than 1000 new documents in 2019 when searching for the phrase "magnetic AND adsorbent" in Scopus (see Figure 1a). In contrast, publishing activity on magnetic separators is rather constant during the last 30 years, with small peaks in the 1980s and since 2010. Most of these documents are published in Chemistry and Chemical Engineering, as well as Environmental and Materials Science journals and describe the synthesis and small-scale testing of a broad variety of magnetic nano- and micro-adsorbents (Figure 1b). Because a detailed discussion of the synthesis and performance of these different types of magnetic adsorbents is out of the scope of this article, the reader is referred to the comprehensive reviews of Mehta, Mazumdar, and Singh [1] and most recently Mohammed et al. [2].

In the following, a rough comparison between the performance and limitations of an adsorption process conducted in a packed bed and with a combination of magnetic micro-adsorbents followed by a magnetic separator is given. The comparison is based on several assumptions regarding parameters like particle diameter, effective diffusivities, specific throughput, etc. Of course, the possible values of these parameters span a certain range, and the values chosen represent a subjective selection of the author based on his experimental and theoretical expertise in both fields, packed beds as well as magnetic micro-adsorbents. Nevertheless, the comparison delivers the order of magnitude of important key numbers, such as space-time yields or cycle times. The comparison is done for two representative scenarios. First, the removal of a diluted contaminant such as heavy metal ions by ion exchange adsorbents, and second, the capture and purification of a larger biomolecule present in the g/L range in the feed stream. The comparison starts by looking at the kinetics of the adsorption process. For this, the characteristic time of the step, which limits the mass transfer rate, has to be calculated. For packed beds, macroporous adsorbents in the size range of several hundreds of micrometers are used. Except for extremely low target concentrations, the mass transfer is limited by intraparticle diffusion and the characteristic time is calculated by dividing the square of the particle diameter by the effective pore diffusion coefficient [3]. Typical values for ion exchange adsorbents result in a characteristic time of around 20 min. If contacted with a constant target concentration in the bulk, the adsorbent reaches approximately 37% of its equilibrium loading within this time. After three times the characteristic time, the equilibrium loading approaches 95%. If we would do the same calculation for a porous micro-adsorbent having a diameter of 2 μm and the same effective pore diffusion coefficient, a characteristic time of only 0.01 s

Figure 1



Statistical analysis of the annual number and topics of publications related to magnetic asorbents. (**a**) Annual number of articles published in the fields of magnetic adsorbents and magnetic separators, respectively. (**b**) Science and Engineering fields of the journals in which the articles are published. The numbers are gained from a search within Scopus using the terms "magnetic" AND "adsorbent" as well as "magnetic" AND "separator" in title, abstract, and keywords. Search date: October 27, 2019.

results, clearly showing that intraparticle mass transfer is not limiting.

In contrast, external mass transfer, saying the diffusion of the target species through the Nernst film surrounding the particle, dominates. In this case, the characteristic time is defined by the quotient of the film thickness and the mass transfer coefficient in the film. Using this definition, we find a characteristic time of the adsorption step of micro-adsorbents in the range of 10 s, which is more than 100 times faster than the conventional ion exchange adsorbent ; however, looking at the complete adsorption and separation process required in the case of using magnetic micro-adsorbents in combination with magnetic separation, it becomes obvious that mass transfer of the adsorption is not the step which determines the space-time yield of the process. Therefore, in the second part of the comparison, we look at the achievable throughputs and the corresponding size of the required equipment. Columns filled with ion exchange adsorbents normally are operated at 10 15 bed volumes per hour (BV/h). Using the unit of BV/h is a convenient way to state the throughput of a column or a separator, independent of its absolute size (15 BV/h means that the feed solution passing the column equals 15 times the volume of the empty column). Assuming a column volume of 1 m^3 and a target concentration in the feed of 1 mmol/L, we get a throughput of 15 m^3/h and a space-time yield of 15 mol/(m^3 h). Finally, assuming a typical adsorption capacity of an ion exchange resin of 2 mmol/mL, we find that the theoretical breakthrough time of the column would be after 133 h, meaning that the cycle time before a regeneration step is needed will be also in this range.

In case of magnetic adsorbents in the µm range and the use of so-called wet high intensity magnetic separators (WHIMS), throughputs of approximately 200 BV/h can be reached, if normalized by the volume of the separation chamber of the separator. In literature, higher numbers can be found; however, one has to keep in mind that separation efficiencies of more than 99.8% are required in the case of valuable micro-adsorbents which must be recycled several hundred times. With a value of 200 BV/h, an aspired throughput of 15 m^3/h could be reached by a magnetic separator having a separation chamber volume of 75 L. The achievable cycle time of the process is determined by the capacity of the particles for the dissolved target but also by the particle separation capacity of the magnetic separator. The capacity of the particles determines the required particle concentration of the adsorption step. At this point, it should be emphasized that in the authors' opinion, there exists no reason why a magnetic version of a micro-adsorbent should show a better capacity than a comparable non-magnetic type of the same size. In fact, it is reasonable that the specific capacity of the magnetic variant is somewhat reduced, simply by the fact that the magnetic component of the composite material requires additional space and brings additional weight. Therefore, a working capacity of the magnetic adsorbent of 1 mmol/g is assumed. In case of our example, this corresponds with a required adsorbent concentration of 1 g/L when mixed with the feed solution. In the following separation step, we have to capture these suspended micro-adsorbents from the treated solution. For particles in the µm range, separation capacities of around 200 g per liter of separation chamber can be reached. A magnetic separator of 75 L chamber volume would be able to hold back 15 kg of particles, corresponding to 15 m^3 of a 1 g/L solution. Therefore, the cycle time of the process using magnetic micro-adsorbents will be in the range of 1 h. In summary, the comparison shows that the process using magnetic micro-adsorbents can be estimated to give superior space-time yields, which are more than ten times higher than those using conventional adsorbents in a packed bed; however, if one looks at the economic

viability of the process, a different picture results. A 1 m^3 ion exchange column operated at low pressure is a rather simple piece of equipment having costs of 10,000 50,000 € depending on material, sensors, etc. On the other hand, a WHIMS having a 75 L separation chamber operating at a magnetic field of around 0.25 T will cost more than 100,000 € and because of the large magnet, the footprint and weight will be in the range of an ion exchange column.

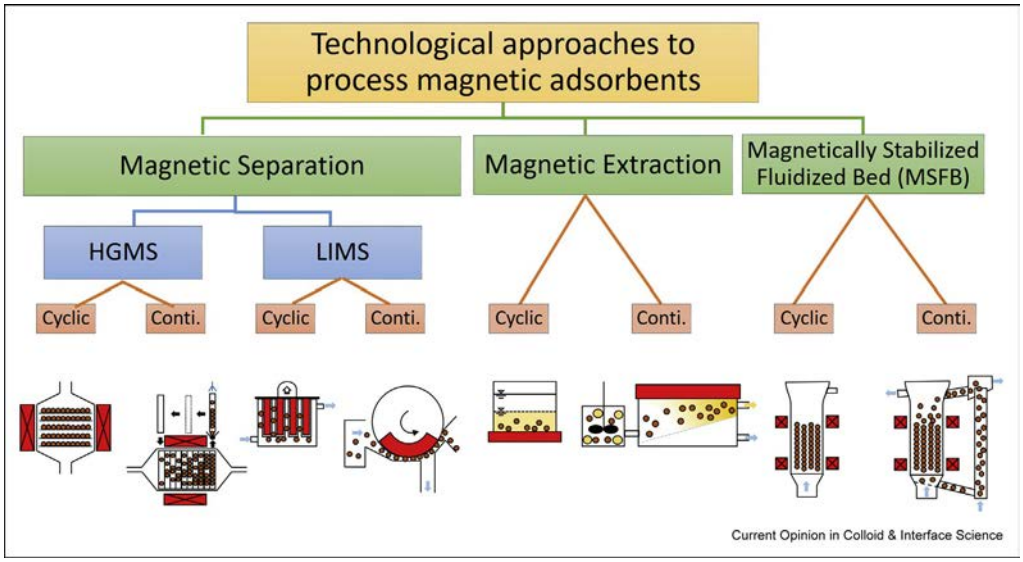
In the following, we will briefly discuss an analogous comparison for the case where an adsorption step is used for the capture of valuable, larger biomolecules. A major difference results from the fact that the effective intraparticle diffusion coefficient of these large molecules is around two orders of magnitude smaller than in the case of small ions. Therefore, the use of large adsorbent particles having diameters of almost a millimeter gets impracticable. In consequence, commercial ion exchange resins used for protein adsorption show diameters of around 90 μm. Because of the reduced diameter, the resulting characteristic time of diffusion stays at around 30 min, which is in the same range as in the first example. As required throughputs are lower in the biopharmaceutical industry, a value of 0.5 m^3/h is assumed, which corresponds to a column volume of 0.1 m^3 at 5 BV/h. For a target concentration of 2 g/L, a space-time yield of 10 kg/(m^3 h) and a cycle time of 10 h result. In case of magnetic micro-adsorbents, the applicable throughput of the magnetic separator stays the same, because particle size and magnetic properties of the adsorbent do not change. Therefore, in order to achieve a throughput of 0.5 m^3/h, a small separation chamber of only 2.5 L will be enough. With 400 kg/(m^3 h), the space-time yield will be around 40 times higher than the one of the ion exchange column; however, the increased target concentration requires a particle concentration of around 20 g/L in the adsorption step. In combination with the high specific throughput of the magnetic separator, this results in a rapid depletion of the particle separation capacity and a very short cycle time of only 3 min. Taking into account that washing, elution, and recovery of the separated particles also take about 5 10 min, it shows that the effective space-time yield of the full process is substantially lower and that the assumed target concentration of around 2 g/L is already close to the upper limit for which the application of magnetic micro-adsorbents makes sense.

Looking at the economics, it can be said that a 100 L chromatographic column withstanding the increased pressure resulting from the reduced particle size and a 2.5 L WHIMS will be roughly in the same price range. As a short summary, it can be said that the economic large-scale application of magnetic micro-adsorbents for small dissolved contaminants like heavy metal ions, phosphate, and arsenic seems hard to achieve using commercially available magnetic separation techniques. In the case of larger target molecules like oligonucleotides and proteins, the result of the comparison is less clear. Additionally, because of their small intraparticle diffusion coefficients, conventional adsorbents have to be reduced in their size and the design of suitable packed bed column gets more demanding and costly. Here, the much larger space-time yields of magnetic separators can make a higher impact and justify the additional effort associated with the sequential adsorption separation process. Nevertheless, several challenges remain, especially the short cycle times, the required very high particle separation efficiencies, and the related high number of adsorbent particle reuses. In the following sections, recent developments of new approaches to exploit the beneficial properties of magnetic adsorbents will be introduced and assessed regarding their potential to overcome some of the limitations stated in this introduction.

New technologies for the application of magnetic adsorbents

A review of the literature about magnetic adsorbents shows that the vast majority of the articles describes an adsorption test conducted with mg amounts in simple batch experiments followed by a separation step using simple handheld permanent magnets. If larger volumes are treated, the separation technique is switched to the application of high-gradient magnetic separators (HGMS) or WHIMS, which are able to separate magnetic adsorbents from larger amounts of feed solution and afterward release them in a concentrated form. Both types of magnetic separators apply a ferromagnetic matrix in the separation chamber, in order to increase the local magnetic field gradients and surface area to which the particles can stick [4]. The main differences between HGMS and WHIMS systems are the applied magnetic field strength and the design of the separation matrix. While true HGMS systems apply magnetic flux densities above 1 T and very fine matrix structures in order to maximize the field gradients, WHIMS normally operate between 0.1 T and 0.5 T and use a more robust, coarse matrix. While HGMS systems are needed for the separation of very fine paramagnetic minerals, superparamagnetic as well as ferri- or ferromagnetic composite magnetic adsorbents can be separated by less costly WHIMS systems at high efficiency. However, classical WHIMS systems designed for mineral and ore industries are not optimized for processes using magnetic adsorbents, especially if the investigated application is in the biotechnological or biopharmaceutical field. Figure 2 is a first classification of new magnetic separation devices, specially designed for pilot- and large-scale recovery of magnetic adsorbents. In the following sections, their most important characteristics and recent examples for their use in combination with magnetic adsorbents will be discussed. A more general review about magnetic separation principles for magnetic beads, which also includes micro-scale separators, can be found in Ref. [5].

Figure 2



Classification of technological approaches to process magnetic nano and micro adsorbents in semi pilot up to industrial scale. HGMS, high gradient magnetic separation; LIMS, low intensity magnetic separation.

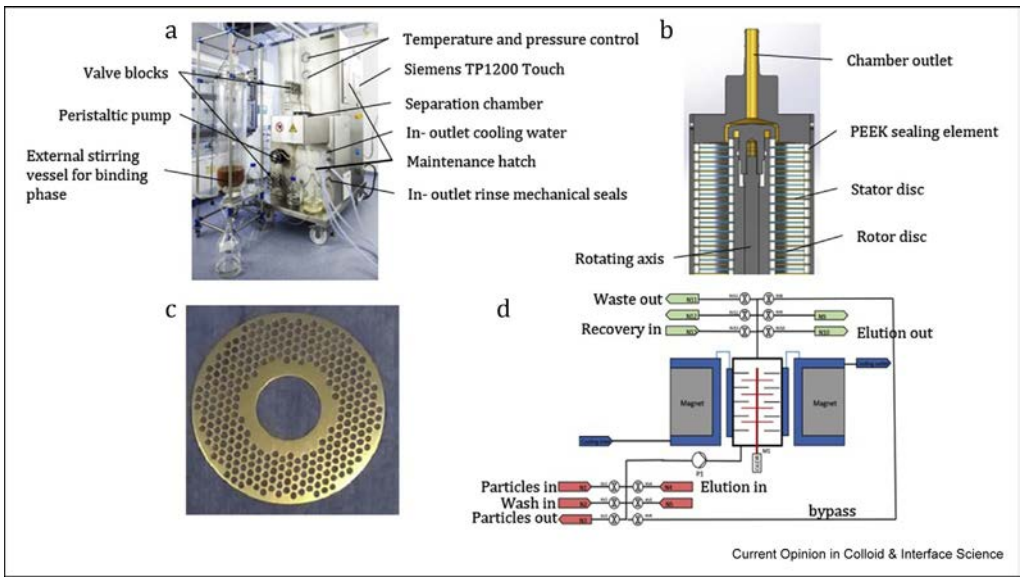
HGMS and WHIMS for adsorption processes

Looking into literature, it becomes apparent that Japan is a hotspot regarding pilot and industrial scale testing of magnetic separation technology for the purification of municipal and industrial wastewaters. As early as 1989, Hoya et al. investigated the purification of storm water overflows by flocculation in combination with magnetic seeding [6]. For this purpose, two pilot plants with a throughput of 1.5 m^3/h and a filtration velocity of 83 m/h were realized. HGMS solenoid magnets with a flux density of 0.3 Twere used. Since then, there are ongoing activities and improvements in this field in Japan which were recently reviewed [7,8]. Among the investigated applications are wastewater from paper industries [9], the removal of arsenic from geothermal water [10], and the removal of iron scale from boiler feed-water in thermal power plants [11]. If these large-scale tests are analyzed, it shows that in the used magnetic separators, magnetite-based adsorbents of around 10 µm are efficiently separated at flux densities between 0.2 T and 0.4 Twith specific throughputs of up to 1900 BV/h, corresponding to filter velocities of 720 m/h in a 50 L HGMS matrix with around 40 cm height. The achieved average matrix loadings are reported to be in the range of 170 g/L. While the particle loading of the separation matrix is very close to the value stated in Tables 1 and 2, the specific throughput is almost an order of magnitude higher; however, one has to take into account that the used magnetite particles are substantially larger than most magnetic adsorbents and that the separation efficiency was in the range of 99%. A loss of magnetic adsorbents of up to 1% can be acceptable in the case of low-cost adsorbents; however, more sophisticated micro- and nano-adsorbents would need higher recovery efficiencies and therefore must be operated at lower speeds. Interestingly, the mentioned large-scale tests used superconducting magnets, although, as mentioned, the applied flux density was usually in the range between 0.2 T and 0.4 T. The reasons for this are that, on the one hand, the tests are mostly conducted by Japanese research groups working in the field of superconducting magnets and, on the other hand, it is likely that beyond a certain magnet size, the use of superconducting magnets is more economic than conventional magnets, even at moderate fields of around 0.5 T.

Magnetic separators tailored for bioindustry

The combination of highly selective magnetic adsorbents with magnetic separation technology allows the capturing of high-value biomolecules directly from the cell culture broth in which they were produced, without the need for preceding centrifugation and filtration steps. The principle is widely established at the small bioanalytical scale; however, the lack of suitable bioindustry-compliant HGMS or WHIMS devices prevented the application of magnet technology-based bioseparation processes in industrial-scale protein purification processes until now. Traditional designs of the separation matrix as well as insufficient sealing concepts cannot meet the rigorous requirements of regulatory authorities for the pharmaceutical drug production, summarized under the umbrella term GMP readiness. Over the last decade, the lack of a GMP-compliant magnetic separation equipment has been tackled by Andritz GmbH in cooperation with the Karlsruhe Institute of Technology, and in 2017 the first GMP-compliant high-gradient magnetic separator MES 100 RS was commercially launched [12,13] (see Figure 3).

Figure 3



First commercial magnetic separator tailored for bioindustrial applications. (**a**) GMP compliant rotor stator magnetic separator MES 100 RS of the company Andritz GmbH. (**b**) Sketch of the separation chamber showing the alternating arrangement of disc shaped elements of the separation matrix. (**c**) Photograph of one of the electropolished disc shaped matrix elements. (**d**) Flow chart of the connected feed streams and possible flow paths within the MES 100 RS. (reproduced from Ref. [12] with permission from Wiley).

Besides having special valve blocks and sealings, the main feature of the MES 100 RS is a rotor stator design of the separation matrix. Instead of wire meshes or grooved plates, the separation matrix consists of electropolished perforated discs. These discs are alternately fixed to the housing or to a shaft in the center of the matrix housing. This brings the advantage that the particles can be efficiently resuspended by a fast rotation of the shaft, without the need of pumping the solution through the separation chamber. In contrast to conventional HGMS systems, this allows washing and elution steps within the separator without flushing the

Table 1

Comparison of the adsorptive removal of diluted contaminants using a packed bed and magnetic adsorbents in combination with a subsequent magnetic separation.

Removal of low concentrated contaminants, e.g. heavy metal ions and nitrate			
Adsorbents in a packed bed		Magnetic micro adsorbent and magnetic separation	
Mass transfer determined by intraparticle diffusion		Mass transfer determined by film diffusion	
Particle diameter d_p	700 μm	Particle diameter	2 μm
Effective pore diffusion coefficient $D_{p,eff}$	$4 \cdot 10^{-10} \frac{m^2}{s}$	Film thickness δ_{film}	$5 \cdot 10^{-4}$ m
		Mass transfer coefficient k_{film}	$5 \cdot 10^{-5} \frac{m}{s}$
Characteristic time of diffusion		Characteristic time of diffusion	
$\tau_{D,PB} = \frac{d_p^2}{D_{p,eff}} = 1220s \approx 20\ min$		$\tau_{D,MS} = \frac{\delta_{film}}{k_{film}} = 10s$	
Adsorption time $3\tau_D$ results in about 95% usage of adsorbent capacity			
Throughput packed bed	15 BV/h	Throughput magnetic separator	200 BV/h
Presumed bed volume (BV)	1 m^3	Separation chamber volume	0.075 m^3
Throughput	15 m^3/h	Throughput magnetic separator	15 m^3/h
Target concentration	1 mmol/L	Target concentration	1 mmol/L
Capacity ion exchange resin	2 mmol/mL	Capacity MA (ion exchange)	1 mmol/g
		Particle capture capacity of the separation chamber	200 g/L
Space time yield limited by the adsorption step	15 mol/(m^3h)	Space time yield limited by the separation step	200 mol/(m^3h)
Total adsorption capacity of the packed bed	2000 mol	Total particle separation capacity of the separator	15 kg
Cycle time until target breakthrough	133 h	Cycle time until particle breakthrough	1 h

Table 2

Comparison of the adsorptive removal of moderately concentrated large biomolecules using a packed bed and magnetic adsorbents in combination with a subsequent magnetic separation.

Capture of medium concentrated products, e.g. proteins			
Adsorbents in a packed bed		Magnetic micro adsorbent and magnetic separation	
Mass transfer determined by intraparticle diffusion		Mass transfer determined by film diffusion	
Particle diameter	90 µm	Particle diameter	2 µm
Effective pore diffusion coefficient	$3 \cdot 10^{-12} \frac{m^2}{s}$	Film thickness	$5 \cdot 10^{-4}\ m$
		Mass transfer coefficient	$2 \cdot 10^{-5} \frac{m}{s}$
Characteristic time of diffusion		Characteristic time of diffusion	
$\tau_{D,PB} = \frac{d_p^2}{D_{p,eff}} = 1620s \approx 30\ min$		$\tau_{D,MS} = \frac{\delta_{film}}{k_{film}} = 25s$	
Adsorption time $3\tau_D$ results in about 95% usage of adsorbent capacity			
Throughput packed bed	5 BV/h	Throughput magnetic separator	200 BV/h
Presumed bed volume (BV)	0.1 m^3	Separator volume	2.5 L
Throughput	0.5 m^3/h	Throughput magnetic separator	0.5 m^3/h
Target concentration	2 g/L	Target concentration	2 g/L
Capacity ion exchange resin	100 mg/mL	Capacity MA (ion exchange)	100 mg/g
		Particle capacity of the separator matrix	200 g/L
Space time yield limited by the adsorption step	10 kg/(m^3h)	Space time yield limited by the separation step	400 kg/(m^3h)
Total adsorption capacity of the packed bed	10 kg	Total particle separation capacity of the separator	500 g
Cycle time until target breakthrough	10 h	Cycle time until particle breakthrough	3 min

adsorbent particles out of the separation chamber. This results in a low consumption of utilities like wash and elution buffers and greatly increases the concentration of the eluted product. Another trend, which can be seen in the biopharmaceutical industries, is the use of so-called disposables for the parts of the equipment, which get into contact with the product. This means that cell cultivation chambers, tubes, filters, cassettes, etc. are for single use. In order to allow the inclusion of magnetic separation steps into this concept, Shaikh and Kampeis developed a disposable HGMS matrix [14]. The separation matrix consists of a plastic bag with tube connectors and filter matrix within. In tests with a filter bag of 140 mL, 5.6 g of magnetic polyvinyl alcohol particles (mean size of 2 µm) could be captured at a flow rate of 150 mL/min. These values convert to a matrix loading of 40 g/L and a throughput of 64 BV/h.

Magnetic extraction

In the Introduction, we have seen that the adsorption kinetics of magnetic micro-adsorbents in the size range of a few micrometers is already very fast. A comparison with the residence time of the particles in current adsorption equipment shows that, with respect to kinetics, there is no reason to reduce the particle size even further; however, things look different when the specific adsorption capacities of the adsorbents are taken into account. Here, magnetic nano-adsorbents often far surpass the value of 100 mg of target species per gram of adsorbent used in our calculation [1,15]. While the switch to nano-adsorbents has the potential to increase the adsorption capacity, it hampers the subsequent separation, especially at a large scale. One way to overcome this dilemma is to separate the nanoparticles by a solvent extraction process instead of a classical magnetic separation. This means that the nanoparticles are entrapped and removed from the aqueous phase by means of immiscible droplets of a second liquid, instead of a solid separation matrix. While in principle, such an adsorption process based on liquid extraction of nanoparticles also works with non-magnetic variants, the use of magnetic nano-adsorbents and the superimposition of an external magnetic field have the potential to greatly enhance the phase separation step in which the dispersed droplets coagulate to a single phase separated from the aqueous solution. The foundation of such an extraction process using magnetic adsorbents was laid by Suzuki et al. [16]. They used a protein friendly aqueous two-phase system (ATPS) in combination with magnetic adsorbents with covalently coupled human immunoglobulin on their surface. By applying this magnetic extraction phase, they were able to capture 90% of the target molecule 'protein A' from a model solution; however, the following elution efficiency of 39% and the achieved purity of 49% clearly showed room for improvement. More than ten years later Becker, Thomas, and Franzreb developed a new type of magnetic extraction phase using a micellar aqueous two phase system (MATPS) in combination with magnetic affinity adsorbents [17]. MATPS can be switched between a single phase state, in which the phase forming polymer is dissolved within the aqueous feed solution, and a two phase state, in which the phase-forming polymer together with the entrapped magnetic

adsorbents form a second phase. The switch between the single and the two-phase state is triggered by a small temperature shift of only a few degrees Celsius. Being able to switch between the one phase and two-phase states enables to conduct washing and elution steps with freely dispersed magnetic adsorbents, greatly improving the efficiencies of these steps. Later, this thermoresponsive magnetic extraction using MATPS was transferred into a continuous process applying flow through separators based on simple flow channels superimposed by a magnetic field generated by a large ferrite permanent magnet [18 21]. Besides protein purification, magnetic solvent extraction has also been proposed for the selective extraction of heavy metals, e.g. Lobato et al. report about the extraction of cobalt ions using a magnetic solvent consisting of an organophosphinic acid into which up to 5 g/L of magnetite nanoparticles, hydrophobized by oleic acid, were mixed [22]. After the uptake of cobalt into the extraction phase and enhanced phase separation applying a magnetic field, the cobalt could be efficiently stripped (>99%) from the extraction phase by 1 M sulfuric acid. Finally, when developing the idea of magnetic extraction phases to its end, it would be nice to have a liquid extraction phase showing significant magnetic responsiveness without the need to add magnetic nanoparticles. In fact, such phases actually exist in the form of single component magnetic ionic liquids (MILs) based on complex cations and/or anions containing strongly paramagnetic atoms. Sajid [23] gives an excellent review about the synthesis and properties of these MILs; however, it also shows that currently all applications are in the field of small-scale sample preparation for analytical purposes.

Magnetically stabilized fluidized beds (MSFB)

At the end of this section about new and emerging technologies to handle magnetic adsorbents in preparative and industrial scale, a third way to contact magnetic adsorbents with feed solutions will be discussed. Besides mixing magnetic adsorbents in a batch reactor, continuously stirred reactor, reaction tube, or the like, and the following solid-liquid separation by magnetic separation or magnetic extraction, magnetic adsorbents can be continuously held in a fluidized state, while the fluidized adsorbent bed is passed by the feed solution. Discussing this way of operation, first the question must be answered why the adsorbents cannot be used in the simple form of a packed bed. The most convincing answer is given in the case of feed solutions containing suspended solids, such as cells and pulp fibers, which would quickly block a packed bed. In addition, fluidized beds result in lower pressure drops than packed beds at fluid velocities above the fluidization point. Additionally, and maybe the most interesting point when discussing MSFB in combination with magnetic adsorbents, the fluidized state offers the possibility of moving the adsorbents counter-currently to the flow direction of the feed solution. Applying this counter-current principle, truly continuous adsorption processes can be designed by using several sequential MSFB for adsorption, washing, and elution. Again, the basic idea of such a process using magnetic adsorbents has been described already in the 1980s by Burns and Graves [24]. Since then, several proof-of-concepts have been shown, however, to the knowledge of the author but not at a larger scale. However, as the recent review by Wang et al. of applications of circulating fluidized beds of non-magnetic adsorbents shows [25], the process concept has a high potential for continuous contaminant removal and bioprocessing.

Promising application areas for magnetic adsorbents

In this section, new developments in the application of magnetic adsorbents will be discussed, which, in the opinion of the author, are of high relevance for current challenges of modern society. Again purely analytical applications will not be considered and the discussion will be restricted to approaches, which have been demonstrated at least in a scale above 100 mL.

Algae harvesting

The increasing importance of algae biotechnology is well illustrated in a letter of leading algae researchers to the editor of Nature Biotechnology [26]. The letter highlights the future prospects of microalgae production as part of a solution for current challenges of modern society. Particularly, microalgae have the highest photosynthetic efficiency among biomass sources (6% compared to max. 3 4%) and they can achieve a CO_2 absorption of 1.7 ton CO_2 per ton of microalgae (http://www.eubia.org). However, because of their small size and low biomass concentration in cultivation ponds, they also present a challenge regarding their separation. Harvesting technologies must be able to treat large throughputs, have low specific energy demands, and achieve high degrees of dewatering of the resulting biomass sludge. Besides centrifuges and decanters, magnetic separators are being investigated for this task. In the process, magnetic micro- or nano-adsorbents having surface chemistries promoting the attachment of microalgae are mixed into the algae suspension. Afterward, the particles with the attached microalgae are captured by magnetic separators and released as a concentrated sludge. Finally, the microalgae are detached by a change in the chemical milieu and the magnetic adsorbents can be washed and reused. In 2015, a review regarding the harvesting of microalgae by magnetic separation was published in the journal Algal Research [27]. Since then, several more publications have shown the potential of this approach for algae harvesting. As an example, Markeb et al. used magnetite nanoparticles functionalized with a quarternary

ammonium group at their surface to introduce anion exchange properties. A small dosage of 0.14 g/L of these magnetic adsorbents was sufficient to harvest more than 95% of the microalgae *Scenedesmus* sp. [28] at a biomass/adsorbent ratio of 2:1. The same harvesting efficiency could be reached for the microalgae *Scenedesmus ovalternus* using bare iron-oxide nanoparticles when the pH of the solution was adjusted to pH 4 [29]. At this pH, the surface charge of magnetite is strongly positive while microalgae keep their negative zeta potential. As a result, the microalgae show a high affinity toward the iron oxide nanoparticles even without specific functionalization.

Phosphate recovery

As in the case of algae, the capture of phosphate by the help of magnetic adsorbents was also originally investigated in the context of eutrophication of water bodies and wastewater treatment. However, phosphate is also a non-substitutable plant nutrient and deposits in which the raw material can be extracted in good purity are running out in foreseeable future, which is why processes for phosphate recovery from industrial and municipal sources are gaining increasing importance. Within the last few years, several new magnetic microadsorbents with high affinities and capacities for phosphate have been developed and their application is demonstrated up to the scale of several hundreds of liters per batch. Drenkova-Tuhtan et al. developed a magnetic nano-adsorbent which is formed as a composite of nanometer-sized Fe_3O_4/SiO_2 magnetic carriers onto which amorphous zinc, iron, and zirconium (oxy-) hydroxides are deposited using a precipitation procedure [30]. Using these particles, more than 1 m^3 of wastewater were treated in a pilot setup consisting of a 200 L batch reactor followed by a two-stage magnetic separation using a drum magnetic separator for primary particle recovery and a small HGMS as second separation stage in order to increase the separation efficiency above 99%. Starting at an initial phosphate concentration in the wastewater of around 10 mg/L PO_4-P, the overall P-recovery efficiency after 20 runs was ~82% and the final eluate showed a 38-times phosphate enrichment. A different chemical route to produce magnetic adsorbents and to attach phosphate by electrostatic interactions has been described by Du et al. [31]. Starting with magnetite particles of around 50 μm, they produce core-shell adsorbents with a hematite shell and a remaining magnetite core by sulfation roasting. Because of the hematite shell, these particles show a strongly negative zeta potential down to pH-values of around 5. For removal, phosphate is precipitated by the addition of CaO in the form of finely dispersed hydroxyapatite and afterward contacted with the magnetic adsorbents. By this procedure, the turbidity generated by the hydroxyapatite precipitation could be reduced to less than 1%.

Removal of diluted contaminants from wastewaters

The removal of dissolved contaminants from large amounts of wastewater is still one of the most widely studied applications of magnetic adsorbents. For this task, many kinds of composites have been suggested, mostly synthesized by surface functionalization of magnetite particles or coprecipitation of adsorbent materials in the presence of magnetic nanoparticles [1]. However, there are also more sophisticated designs such as magnetic metal organic frameworks [32,33] or magnetic zeolites [34]. Focusing on recent investigations using magnetic adsorbents for wastewater treatment in a larger scale, one interesting article of Salinas et al. [35] could be found describing how they synthesized magnetic clays by mixing bentonite with freshly precipitated magnetite nanoparticles, centrifuging the resulting composite particles and drying them at 90 °C for 24 h. Using an adsorbent dosage of 10 g/L and an average residence time of 10 min, they were able to remove 60% of the azo dye concentration (250 ppm) of an industrial wastewater from textile manufacture. Muliwa et al. investigated the removal of Cr(VI) in a continuous adsorption/magnetic separation setup using polypyrrole magnetite nanocomposites and a simple magnetic trap including five NdFeB permanent magnet rods made by Eriez [36]. Applying an adsorbent dosage of 385 mg/L, the initial Cr(VI) concentration of 20 mg/L could be completely adsorbed within an average residence time of 20 min. Although the throughput of the magnetic trap was only around 7 BV/h, the separation efficiency of the nanocomposites did not exceed 80%. This efficiency could be increased to 92% by the packing of steel wool into the separation chamber of the magnetic trap. A current and broader survey of the application of magnetic adsorbents for removal of heavy metals from wastewater is given by Tamjidi [37].

In most cases, the removal of dyes, heavy metals, and other contaminants of industrial origin will be conducted for moderate wastewater amounts and within the well-defined and equipped surrounding of a production site. In this case, the application of magnetic adsorbents is in direct competition with classical adsorption processes applying packed bed technologies, optionally combined with prefiltration, if the feed solution contains suspended solids. These technologies show a mature stage of development and, as the missing commercial applications of magnetic adsorbents in this area show, are hard to beat by new processes requiring an additional separation step. This situation may be different in new challenges modern society is facing. There are several scenarios, where contaminants are spreaded over very large liquid volumes, which are hard to treat by conventional technologies. Here, technological approaches mixing magnetic adsorbents into these large volumes and efficiently recollecting them by magnetic means may be beneficial. Such widespread

contaminants include oil disasters, radioactive substances, or microplastics. Mirshahghassemi et al. report about removal of oil (0.15 g/L) by the application of polyvinylpyrrolidone-coated magnetic nanoparticles and the application of a simple HGMS setup using permanent magnets and a steel-wool matrix [38]. During a process time of 7 h, more than 1500 BV could be treated with a removal efficiency of more than 80% and without any significant loss in performance. Also, in this case there is a current review available discussing the efficiency of different types of magnetic adsorbents for oil spill removal [39]. Microplastic loads in rivers and effluents of municipal wastewater treatment plants are getting into the focus of the discussions about important sources for this thread. Looking for possible removal processes, the application of magnetic adsorbents is one of the most easily scalable approaches. In 2019, two articles were published in which potential adsorbents are introduced. Misra et al. developed a magnetic polyoxometalate supported ionic liquid phase which was able to completely remove a concentration of 1 g/L polystyrene beads of 1 μm size at an adsorbent dosage of 10 g/L [40]. Rhein et al. demonstrated a removal of up to 95% of 6 μm polymethyl methacrylate (PMMA) particles by seeding of approximately 0.4 g/L natural magnetite having a mean diameter of 2.7 μm at a volume ratio of PMMA:magnetite of 1:1 [41].

Protein purification

Finally, the current status of the application of magnetic adsorbents for the purification of proteins, viruses, or cells in preparative or industrial scale shall be discussed. As was shown in the Introduction, a rough performance and cost comparison between conventional protein purification using chromatography resins in a packed bed and the use of magnetic adsorbents in combination with magnetic separation does not result in conclusive information on which process technology is preferable. Nevertheless, the capture of valuable proteins after their production in a fermentation or cell culture process is well suited for the application of magnetic adsorbents for several reasons. First, the fermentation or cell culture broth always contains a high degree of suspended solids formed by whole cells or cell debris of disrupted cells. Therefore, packed bed chromatography always requires centrifugation and filtration steps as pretreatment, while the protein adsorption using magnetic adsorbents can be done directly in unclarified feed stocks. Second, proteins are large biomolecules showing low pore diffusivities in chromatographic media. Therefore, the much faster kinetics of small porous or even nano- and micron-sized non-porous magnetic adsorbents have an impact on the achievable space-time yields of the processes. Third, proteins are often prone to unwanted enzymatic degradation, oxidation, etc. in the original fermentation or cell culture broth. Therefore, a fast capture and stabilization of the target protein is essential for the process yield. Here, the fast and simultaneous protein capture by mixing an adequate amount of magnetic adsorbents directly into the broth brings an undeniable gain in time. Fourth, current research findings show that not only the capture time should be minimized but often also the time the protein stays in a bound state on the adsorbent [42]. In this respect, the short cycle time of the process using magnetic adsorbents turns into an advantage. The listed points show that in case of protein capture, there are several reasons that may favor the use of magnetic adsorbents, next to the basic increase in space-time yield. However, before biopharmaceutical industry can apply this technology, suitable process equipment and economically competitive magnetic adsorbents are required. In both fields, important progress has been achieved in the last few years. As shown in the section about magnetic separators tailored for bioindustry, the first GMP conforming HGMS has been commercialized [12,13,43]. Recently, Ebeler et al. showed that applying a common cleaning in place procedure using 0.5 M NaOH, the criteria of 10 ppm residual protein in the complete separator, often demanded for GMP production, could be easily reached [44]. Using precursors of the Andritz magnetic separator, several research groups could show the effectiveness of the rotor stator concept for protein purification [45 48]. In the case of macroporous adsorbents in a size range above approximately 30 μm, Brechmann et al. introduced a prototype of a magnetic separator using magnetic rods for particle separation. After separation, the particles are flushed into an external vessel in which the elution takes place in a packed bed mode. Using their separator and magnetic protein A agarose beads with a mean diameter of 90 μm, they demonstrated a pilot-scale process for monoclonal antibody purification directly from unclarified cell culture broth. The results show that, on one hand, the external elution clearly reduces the required amounts of elution buffer and increases the resulting product concentration. On the other hand, packed bed elution will not be practicable in the case of magnetic adsorbents with micrometer or submicrometer size.

As important as the process equipment is the availability of magnetic adsorbents suitable for industrial applications. Here, it is important to note that several well-known suppliers of chromatography media, such as GE Healthcare, Thermo Fisher, and Merck Millipore, also provide an increasing selection of magnetic adsorbents. Besides these commercial particles, Schwaminger and Fraga García recently published several examples that bare iron oxide nanoparticles can be excellent magnet adsorbents, when tailored peptide tags with high affinity toward iron oxides are fused to the target protein [45,49 51]. Gomes et al. demonstrated that magnetic hydrophobic-charge induction adsorbents could reach an impressive loading capacity of up to 180 mg of immunoglobulins per gram of magnetic adsorbents when applied in clarified rabbit serum. For a more comprehensive overview of recent developments in the

synthesis and application of magnetic adsorbents in bioprocessing, the reader is referred to an excellent review by Schwaminger et al. [52].

Concluding remarks and future perspectives

Selective separations using magnetic adsorbents are a very active and broad research field. Currently, magnetic adsorbents for almost all classes of dissolved or colloidal substances have been described and the proof-of-concept of a sequential process using an adsorption and/or flocculation step followed by a magnetic separation of the loaded adsorbent from the treated solution is shown in small scale. Nevertheless, besides the MIEX technology developed by Australian scientists from CSIRO and the company Orica [53], the author is not aware of any large-scale industrial separation process using magnetic adsorbents. From the references and the corresponding discussions listed above, it becomes obvious that the use of magnetic adsorbents in the field of bioprocessing seems to be the field where the leap to commercial application seems most likely. Besides the industrial purification of proteins, this seems especially true for the emerging fields of large-scale capture and purification of viruses or specific cells. In these fields, conventional chromatography is not applicable and, what is even more important, magnetic capture technologies are state of the art at small preparative scales, as is needed for example for the obtaining of bone marrow stem cells for leukemia patients (https://www.miltenyibiotec.com/DE-en/products/cell-manufacturing-platform/clinimacs-prodigy.html). Besides the capture and purification of cells used for therapeutic purposes, there are also interesting approaches aiming for the removal of pathogenic compounds from body fluids [54,55]. In all of these cases, magnetic adsorbents with high affinity and selectivity are used to mark the target cells and allow their highly effective capture from cell suspensions, which contain orders of magnitude more cells, which are not marked and can freely pass the magnetic separator. It is this type of application, requesting a selective separation of a specific cell or particle type from a surplus of comparable solids, in which magnetic sorbents and suitable magnetic separators can play off their uniqueness.

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- * of special interest
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