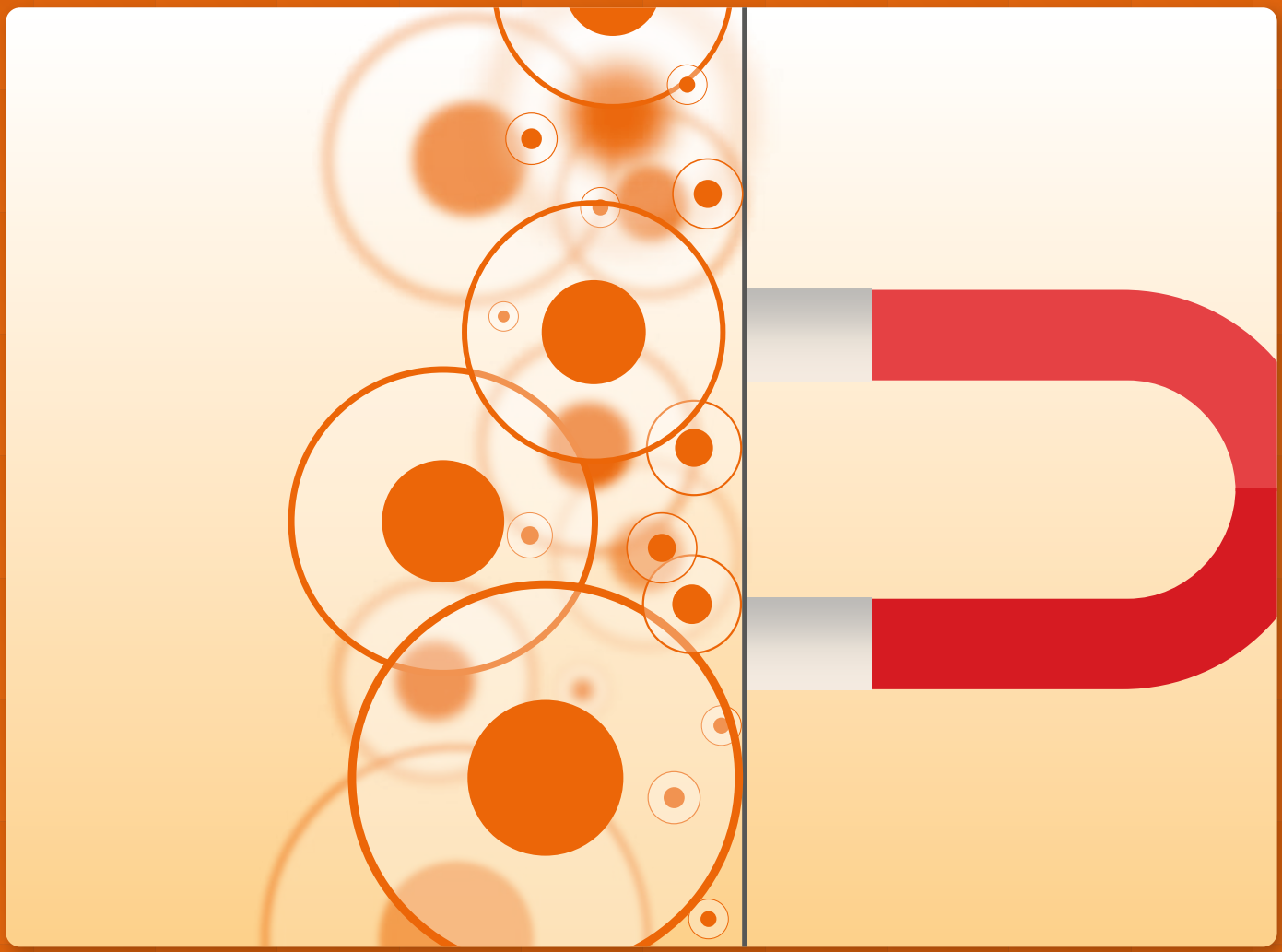
The Advanced Guide to Set Up Biomagnetic Separation Production Processes



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SUMARY

Introduction. The Use of Biomagnetic Separation in Production Processes

Magnetic separation is a breakthrough technique for in vitro diagnostics (IVD). Scientists, hospitals and companies have taken advantage of magnetic separation for immunoassays, molecular diagnostic and genetic testing systems and kits. However, this type of technology is typically utilized by the end-user in very small quantities.

When scaling up production processes, if one simply uses larger magnets or classical magnetic separators, the process will inevitably lead to in-lot inconsistencies, high material losses of both beads and biomolecules, aggregation of the beads and safety issues. In fact, accidents from a lack of attention to safety issues have been reported and are not rare.

Unless one uses homogenous biomagnetic separation conditions from the very earliest developmental steps, the cumulative experience will be useless when volumes are scaled up. The information will not translate to larger volume production processes. In addition, if you do not know all of your conditions, you cannot use the same principles and biomagnetic separation techniques that you have been using in the lab when you go to production. Therefore, production managers should take care to know all of the conditions product developers are using – not just the separation time variable for one specific device. To go to production, you must know all of the experimental conditions you rely on in the lab. If all you have monitored is separation time, it will not be enough information to allow those who need to scale up production to do so.

This guide will try to explain how the production process involving magnetic beads can be smoothly and efficiently scaled up using homogenous biomagnetic separation systems such as SEPMAG, as opposed to using classic magnetic separators or simple magnets. This guide will show how important all of the lab conditions are in order to have efficient and clean large scale separations.

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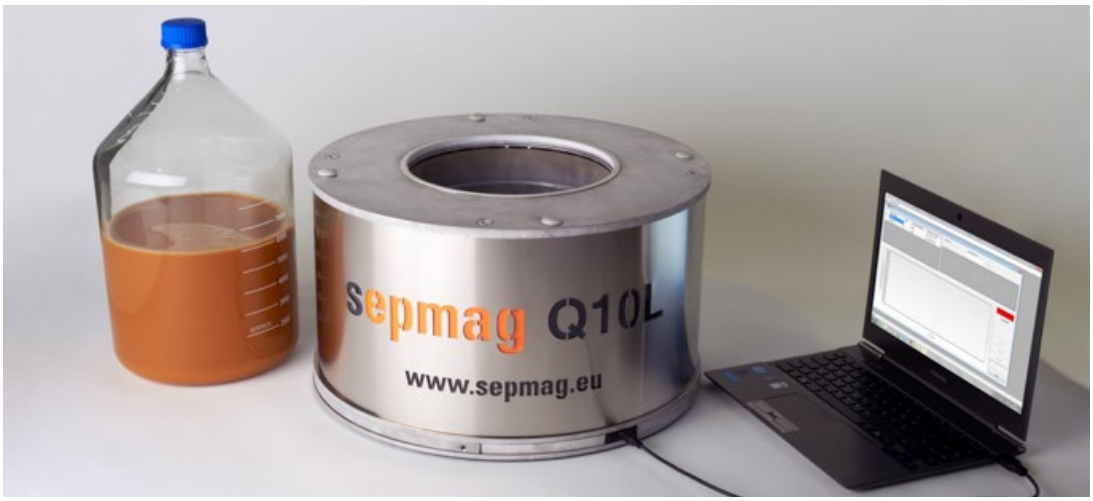

1. How Biomagnetic Separation Helps You Forget the Nightmare of Centrifugation and Filtering

Biomagnetic separation techniques are faster, cheaper and easier to use than non-magnetic techniques. In addition, when biomagnetic separation techniques are performed under homogenous conditions they are also scalable and easily validated.

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In general, life science companies have great expertise in coating (mostly non-magnetic) beads and surfaces. They attach biomolecules, DNA, etc. to surfaces easily. Production teams will have much experience setting up the process to attach these biomolecules to magnetic beads because the technologies are very similar to attaching to non-magnetic microspheres or other surfaces.

When using non-magnetic beads for attachment, the separation processes include centrifugation and filtration (either classic or tangential filtration) in order to separate the solids and discarding the dirty supernatant. One then washes with clean buffers several times to gain the final product. Anyone in the lab can tell you about the problems of these techniques:

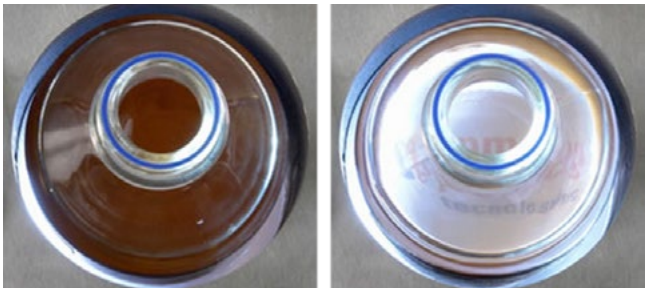
1. When using classic filtration techniques filters can clog and the performance of the filters vary with time and usage.
2. When using tangential filtration techniques the warm-up time can take hours and it is difficult to establish the best balance between flow, temperature and pressure.
3. When using centrifugation, resuspending the centrifuged solids can be a very dirty job and maintenance of the centrifuge is very costly.

If the beads are magnetic, however, the use of biomagnetic separation systems provides a sound alternative:

- Quick process (just a few minutes)
- Clean (no buffers or filters to change)
- No maintenance because there are no moving parts
- No costs associated with running a device that uses permanent magnets

The main drawback in biomagnetic separation is the lack of control over the process. Standard magnetic separators do not have well-defined conditions. With the more classic separation techniques listed above, you can define the parameters of the processes well, but with a standard biomagnetic separator only the time of separation associated with a specific device is typically noted as a variable in the process.

But with modern homogenous biomagnetic separation systems such as SEPMAG, separation conditions are known and can be reproduced regardless of the volume. This allows you to not only take advantage of the typical benefits of biomagnetic separation (i.e. ease of separation and cost advantages), but also allows you to easily validate and scale up the process.



2. The Two Characteristics that Guarantee Lot-to-Lot Consistency of Biomagnetic Separation

If one wants to scale up production from small lab lots to full-scale large lots, non-homogenous biomagnetic separation techniques will result in lot-to-lot inconsistencies. Homogenous biomagnetic separation conditions, however, guarantee consistent results regardless of production scale.

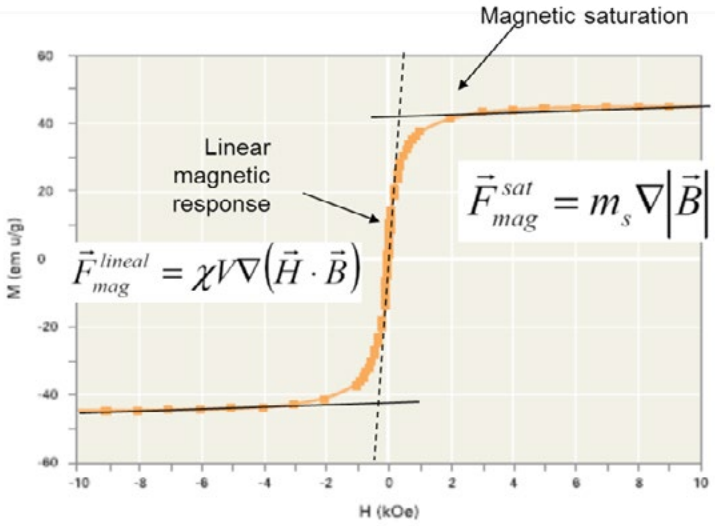
In order to have consistency from a small lab scale to a large production scale, it is vitally important to have well-defined conditions. Unfortunately, if the biomagnetic conditions are not homogenous (i.e. by using simple magnets or classical magnetic separators), it is difficult to determine production conditions and to therefore have large-scale production results that are consistent with the results determined during development (i.e. during small scale production). You are using different devices with different conditions and the separation processes will not be the same. Scaling up almost always results in greater material losses and irreversible greater aggregation processes.

Homogenous biomagnetic separation devices like the SEPMAG systems achieve consistency by imposing two important conditions:

1. The devices magnetically saturate the beads by applying a field higher than 0.1 Tesla. That would be enough to saturate magnetite. For other magnetic pigments the field value may differ.
2. The devices generate a well-characterized and constant magnetic field gradient.

By fulfilling these two conditions, the force is guaranteed to be the same across all of the beads, regardless of their position in the separation vessel. When the field is small, the magnetic susceptibility is constant (i.e. the magnetic moment depends linearly with the field) and it is difficult to get a homogenous force. When you magnetically saturate the beads, the magnetic moment is near constant, the gradient is constant, and then the force on each bead will be independent of volume. This allows for significantly less to no material loss and significantly fewer to no irreversible aggregation problems.

Because of these conditions and the lack of material loss, consistency in production batches is therefore, guaranteed. No additional process development is necessary in order to achieve consistency. No additional resources and effort is required to find production conditions. Homogenous biomagnetic separation necessarily leads to a final product that is consistent with the laboratory specifications.



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3. Keeping Bead and Biomolecule Losses near Zero during Production

When scaling up a process using a non-homogenous magnetic separator, the percentage of bead and biomolecule losses significantly increases with an increase in volume. One way of dealing with this problem is by applying a higher force at longer distances. But for this to work, you must apply this greater force without increasing the forces in the retention area in order to avoid irreversible aggregation. A homogenous separator exerts the same force on all beads regardless of their position in the vessel, allowing the technician to use lower magnetic forces during the process. Under these conditions material loss and aggregation are mitigated.

In standard magnetic separators, the magnetic field decreases with distance and the force decreases even faster with distance. Therefore, in a large scale production, fewer beads are captured with the same separation time used in smaller scale productions. Since the force decreases more quickly than the distance the beads travel, time needs to be increased by orders of magnitude (near exponential increases) in order to maintain a constant level of loss.

In order to avoid these material losses by maintaining the same force value over the beads farthest from the magnet when the volume of the vessel is changed, your beads will experience much higher retention forces at the walls of the vessel. In addition, the time of separation will need to increase as the distance the beads need to travel increases in larger vessels. However, when you have higher retention forces over a longer period of separation time, you increase the risk of irreversible aggregation.

In addition to these problems with classic magnetic separators, the cost and weight of the separator scales up much more quickly than the useful working volume increases.

The only way to overcome these significant material losses from standard biomagnetic separators is to switch to more modern systems that generate homogenous force conditions regardless of the distance from the beads to the magnet. Since the force is constant over the entire volume, losses are constant and the separation time will be linearly dependent on the distance the beads need to travel. Since the retention force is much lower than when using classic separators, the risk of irreversible aggregation is much lower.

One additional advantage of homogenous biomagnetic separation systems such as SEPMAG is that although the cost and weight of these systems increase, they increase much less than the rate of increase in productivity after scaling up.

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4. Objectively Quantifying the Separation Time of your Biomagnetic Separation Process

The separation time in standard magnetic separation devices is usually determined by analyzing aliquots of solution taken at different times. The problem is that each aliquot gives the technician information about one spatial point in time. Therefore, the design of validation experiments becomes a very complex endeavor. Homogenous systems can be monitored, however, as a whole, allowing the technician to monitor all points at all times during the process. Monitoring the entire process provides an easy and objective quantification of the separation time parameter.

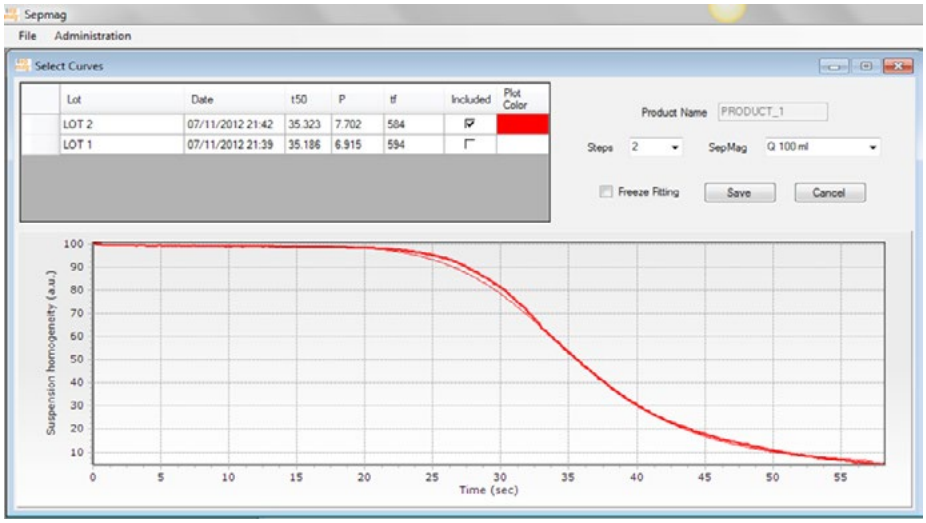
The separation time is the time between when the vessel is placed inside the biomagnetic separator and before the supernatant is pumped out. This is a practical value that should be followed by production technicians and that should be used in any standard operating procedure (SOP). But determining this value in classic, inhomogeneous magnetic separators is not straightforward. The magnetic beads move at different speeds at different points in the vessel. In order to determine an SOP for these inhomogeneous separators, it is necessary to sample the beads at different spatial points and times. This requires a complex and expensive validation experimental design for each individual product in order to have reliable results.

In contrast, homogenous biomagnetic separation conditions such as those provided by SEPMAG technology allow all beads to move at the same speed, since the force is constant over the entire working volume of the vessel. The bead front moves radially and can be easily monitored and quantified. Optical measurement can be accomplished over the entire suspension volume, eliminating the need for complex sampling protocols.

Monitoring systems such as the SEPMAG QCR provides a standard separation curve, making it much easier to quantify separation time. Since the curves are typically sigmoidal-like, the half separation time (t50) is the suggested ‘robust’ measurement. A direct measure at 99% separation is possible, but there is more signal noise, decreasing the accuracy of the measurement.

In practice, separations times that are 3-5 times greater than the half separation time will give > 99% recovery. If it is necessary for the purposes of validation, traditional sampling can be performed in order to fine tune the separation time. In homogenous biomagnetic separation, because of the constant speed of bead movement and a standard protocol to determine the initial separation time, sampling experiments are straightforward and the size of validation experiments is minimized.

Monitoring homogenous biomagnetic separation processes provides a robust way to determine and validate separation times both at small scale development and scaled up production processes



5. How do you determine the Right Separation Time during Production?

When one scales up production using a classic magnetic separation system, one finds that the separation time increases quickly with an increase in production volume. An increase in separation time means that material losses are higher and aggregation problems become a serious problem. By using homogenous separation time, one finds that the separation time is shorter and can be easily estimated. In homogeneous systems material loss and bead aggregation is minimized.

Standard magnetic separators generate inhomogeneous magnetic forces and fields. When production is scaled up, the inhomogeneity increases even further. Magnetic beads far from the magnet move much more slowly than those closer to the magnet. If you increase the force and/or separation time in order to capture the beads far from the magnet, you will increase the risk of irreversible bead aggregation in the beads that start near the magnet wall.

In contrast, homogenous biomagnetic separation systems can generate the same force regardless of the scale of production or model of device. Since forces can be kept constant when moving from R&D to production (i.e. development using a SEPMAG A in the lab to production using a SEPMAG Q), the beads are in the same state and experience the same forces in each device. When we maintain the same force on the beads, the beads will move at a constant speed in both the R&D lab and the production line.

Since the beads are moving at a constant speed, we can calculate the correct separation time for a production process (based on maintaining losses as low as those experienced in the R&D lab while not increasing the risk for bead aggregation). The calculation is straightforward:

$$t_{prod} = t_{lab} \frac{d_{prod}}{d_{lab}}$$

Therefore one can, for example, use a 50 ml centrifuge tube with a diameter of 30 mm in a SEPMAG A125 ml device. The optimal separation time (with losses below 1% and no resuspension problems) is determined in the lab to be 65 seconds.

If one moves the same process to a SEPMAG Q1L device using 1 Liter bottles with a radius of 55.5 mm and the same concentration of beads, the estimated separation time will be 65 * 55.5/30 = 109 seconds.

Therefore, homogenous biomagnetic separation conditions guarantee consistency regardless of volume and enable developers to easily determine the optimal separation time for their product (i.e. no material loss and no irreversible aggregation) at each volume.

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6. Avoiding Irreversible Aggregation Problems during Production

In-lot consistency is the key to reproducibility at the level of a kit. Unfortunately, in non-homogenous systems irreversible aggregation is one of the main sources of in-lot variability. If all of the beads are exposed to the same force as they are in homogenous magnetic systems, the risk of aggregation is greatly reduced.

Standard magnetic separators generate field profiles that always lead to forces that vary with distance. Therefore, magnetic beads far from the retention area experience very low forces and need longer times exposed to the forces in order to be separated. Magnetic beads that start near the retention position experience large forces for long periods of time during this separation period. High forces over long exposure times lead to a high risk of irreversible aggregation which results in substantial in-lot inconsistency.

In large volumes technicians and scientists can attempt to disaggregate beads that have aggregated during the separation process by using the sonication method as part of the resuspension protocol. Unfortunately, as volumes increase, disaggregation becomes more complex and less efficient. When testing beads functionally after separation, beads that were aggregated or are still aggregated perform very differently than beads that have never aggregated. As a consequence, different aliquots from the lot such as those in single kits can be functionally inconsistent.

Homogenous biomagnetic separation systems such as SEPMAG systems, apply the same force over all of the beads regardless of where they are in the vessel. Since the forces on the farther beads are higher than in classic separators at long distances, the farthest beads separate quickly and the separation time is short. In the retention area, the force is large enough to retain the beads, but since it is constant relative to distance from the magnet, it can be lower than in standard inhomogeneous devices. Therefore, moderate forces over a short exposure time leads to no risk of aggregation and a guarantee of substantial in-lot consistency.

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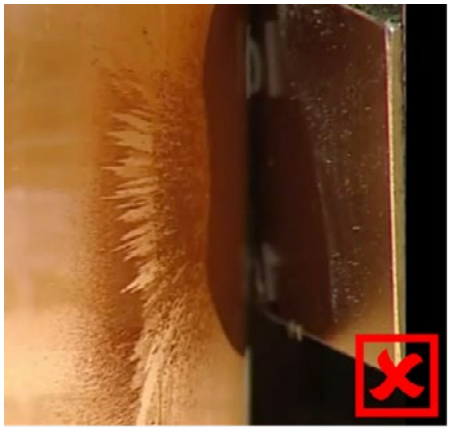
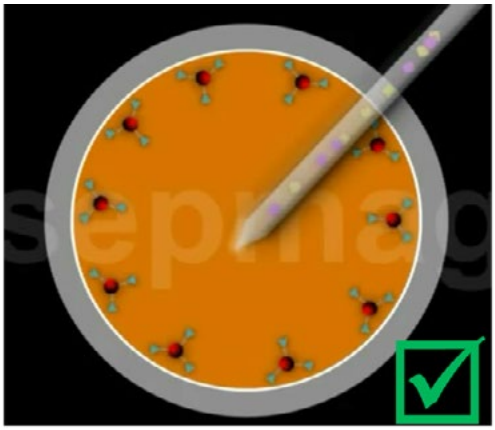




7. How to Detect Resuspension Problems with Biomagnetic Separation Processes

Due to the inherent properties of classic non-homogenous biomagnetic separators, beads can aggregate during the separation process. When this happens, technicians try to resolve the problem by using special resuspension techniques like the sonication method . But problems with resuspension can ultimately lead to end-product variability, especially if aggregation is not detected early. Under homogenous biomagnetic separation conditions, aggregates will move more quickly than individual beads and therefore the perceived separation time is shorter than expected. If one can continuously monitor the separation process, the technician can be alerted to aggregation problems early in the process.

One of the major problems with aggregated beads is that parts of the surfaces of these compromised beads are not functionalized with the biomolecule of choice (e.g. antibodies, antigen, genetic material, etc.). Optimizing the forces by using homogenous biomagnetic separation will help to minimize aggregation risk. If a lab uses a coating that has a high tendency to aggregate, special resuspension steps such as sonication may be necessary, but usually with gentle separation systems like SEPMAG, rolling the beads is enough to gently disaggregate and resuspend them.

Currently aggregation problems are detected when the biofunctionality of the kits is checked either just before conjugation or at the very end of the process. Detection of aggregation problems at these steps delays the ability of the investigator or technician to take corrective actions in a timely manner or begin a new batch if the aggregation problems are too large.

In addition, the typical steps of biomagnetic separation include several washes after or between bio-functionalization steps. After each of these steps, a biomagnetic separation is performed. If the process is monitored and biomagnetic separation is homogenous, aggregated beads will move more quickly than non-aggregated beads. Theoretically and in practice, aggregated beads essentially act as larger magnetic beads (larger bead diameter = larger magnetic moment). When this happens, the time it takes to separate the beads will be shorter than calculated by the standard curve. In addition, if the concentration of the beads is not changed from wash to wash, the separation time will be shorter in each successive biomagnetic separation step because the aggregation is cumulative.

It is important to note that the risk of aggregation will never be zero. But early detection would allow technicians to take immediate corrective action before performing the expensive coating or conjugation steps with costly biomolecules. Sometimes this corrective action can be as simple as repeating the resuspension process. Monitoring would save time and needless added cost of discarding large batches that fail QC due to in-lot inconsistencies, the normal consequence of detecting aggregation problems too late. SEPMAG technology provides monitoring in real time which circumvents added costs and other problems due to bead aggregation in non-homogenous systems.

If the process is monitored and biomagnetic separation is homogenous, aggregated beads will move more quickly than non-aggregated beads.

8. The Three Key Parameters for Defining a Production Process in Biomagnetic Separation

If scientists and technicians link their production results solely to the separation time on one specific piece of classic biomagnetic separation equipment they will not be able to translate that success to different batch sizes or even the same batch size on a different piece of equipment unless they optimize the separation time for the new conditions. Instead, one can choose a more modern homogenous biomagnetic separation system such as SEPMAG that allows you to work with different batch sizes and therefore, allows you to easily scale up your process.

The main production parameter used in classic magnetic separators is the separation time. This separation time is dependent on the piece of equipment and on the scale of production. The process cannot be reproduced with different equipment and cannot be reproduced on a different scale. When production needs to be altered, the magnetic separation step will become the bottleneck because you will have to redefine the parameters in order to change scale.

In order to overcome these problems, the production process should be performed with a system that has well-defined biomagnetic separation conditions (e.g. SEPMAG systems). With homogenous biomagnetic separators, the conditions are standardized and well understood and the process can therefore be replicated in different systems and in different volumes.

You can define the biomagnetic separation process by determining three simple parameters:

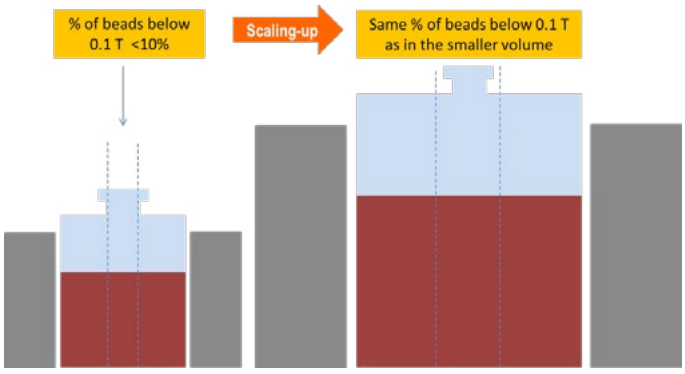
1. The value of the constant magnetic field gradient. In homogenous separation systems, this value is provided by the manufacturer and can be found on the technical data sheet.
2. The maximal percentage of beads that are initially in suboptimal conditions. If based on magnetite, use the formula % of suboptimal beads 100* = (2* (0.1/gradient)/vessel diameter)2. For other magnetic pigments, substitute 0.1 by the correct saturation field in Tesla.
3. A separation time large enough to allow an acceptable level of material losses. Since there is no risk of irreversible aggregation in homogenous biomagnetic systems, the time can be increased a bit to reduce losses if necessary.

With these parameters known, you can scale your production process either up or down with the same percentage of recovery and with no aggregation problems. SEPMAG technology is the only commercially available technology that can account for all three of the above parameters and that also allows users to control these parameters.

In addition, if the amount of beads not saturated at the start of the biomagnetic separation is small (<10%), you can reproduce the validated process in future biomagnetic separations by:

- Having a magnetic field gradient no higher than the defined field gradient. This ensures that all the beads experience the same force as when the parameters were defined and avoids the risk of irreversible aggregation.
- Keeping the % of magnetic beads below saturation (Bs) at the initial starting moment of separation equal or less than the defined value, applying the formula and conditions of the new system.

When one uses homogenous biomagnetic conditions the defined nature of the separation step guarantees lot-to-lot consistency even at different volumes. Therefore, scaling up a process is straightforward.



9. How Early Monitoring of Homogenous Biomagnetic Separation detects QC Issues

In non-homogenous magnetic separators, monitoring the entire separation process is difficult to impossible. As a result errors in the process such as using the wrong magnetic beads or using buffers with the wrong properties are not detected until the final QC testing stage. But homogenous biomagnetic systems can be monitored from start to finish of the separation process. Technicians can watch for changes in the projected separation time and, if a deviation is detected, can immediately take corrective actions.

The production of magnetic bead-based products is comprised of many steps including incubations, washings, conjugations, etc. If a mistake is made in any one of these steps, the entire lot can be jeopardized. Functional QC tests are expensive, so they are typically performed only at the end of the production process, if the SOP is followed with no mistakes. If errors happened during the process, therefore, they are only detected at the very end of production.

In homogenous biomagnetic separation processes, the magnetic force is constant and the force is defined by the magnetic field gradient, therefore, the percentage of magnetic beads initially in suboptimal conditions is small and the separation time is short. If these production parameters are fixed, the separation time would then depend solely on the suspension characteristics including:

- Magnetic bead characteristics of size, magnetic charge and surface charge
- Concentration of magnetic beads
- Suspension viscosity, pH and/or ionicity

Using a continuous optical monitor like the SEPMAG QCR to check the opacity of the liquid, the separation time can be objectively measured and compared to a standard curve. Deviation from the expected curve would indicate that something is wrong, allowing technicians to take immediate corrective actions if possible. If not, the batch can be discarded, saving the cost of performing additional steps and allowing technicians to start a new batch earlier. This avoids or minimizes delays in product delivery.

It is important to note that not all QC issues can be detected. But some of the most critical QC issues (e.g. the use of wrong beads or the wrong bead concentrations not matching specifications) that the SEPMAG QCR detects can dramatically affect the IVD kits performance.

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10. The Effect of Magnetic Bead Concentration in Biomagnetic Separation

The concentration of magnetic beads is an important step in biomagnetic separation. Separation time is dependent on magnetic bead concentration, Final kit performance is also very dependent on accurate concentrating techniques, but liquid handling inaccuracies can lead to serious errors. If these concentration errors are not detected early in the process, excessive time, money and effort will need to be spent to either correct or redo the batch.

The correct concentration of functionalized magnetic beads is very important for final kit performance (e.g. in immunoassay kits or molecular diagnostic kits). Liquid handling, especially in large volumes, can be very tricky – even a graduated cylinder has a precision of only 2% or less. Therefore, even with strict observance of SOPs, the concentration can be variable, especially when the process involves many buffer changes.

For well-defined homogenous biomagnetic separation processes, the behavior of the process will be dependent on the concentration of beads. Higher concentrations of beads result in a shorter separation time (approximately as the fourth root). This relationship is explained by the collective nature of bead movement. The closer the beads are to one another (higher concentration), the easier they form long, fast-moving chains.

Advanced optical monitoring of homogenous biomagnetic separation processes, for example using SEPMAG's QCR system, can help to detect concentration errors. For example, a 10% change in concentration will modify the separation time by 2.6%. When one compares the current batch curve with a standard curve, it will typically show a shorter half-width time (t50) and steeper change in behavior if the concentration is higher than the specifications. Alternatively, the change in behavior will be smoother and the t50 larger if the suspension is more dilute than the specifications.

Concentration errors can be readily and uniquely detected apart from other sources of errors by optically monitoring the process. The errant batch can be stopped shortly after the magnetic separation step and technicians can take corrective action early or start a new lot, saving time, energy and money.

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11. The Safe Use of Biomagnetic Separation Systems in Production Facilities

Large magnetic systems create potentially high risk environments in terms of safety. These systems generate large magnetic fields which result in the generation of large stray fields. The stray fields affect the surrounding environment and can attract ferromagnetic objects, potentially injuring system operators. The larger the system, the higher the risk, especially if workers do not follow Health and Safety protocols. As a result, large costly safety areas are necessary to help protect the safety of workers with non-homogenous biomagnetic devices. Homogenous biomagnetic separation systems, on the other hand are intrinsically safe, generating very small stray fields that alleviate the necessity for large safety zones.

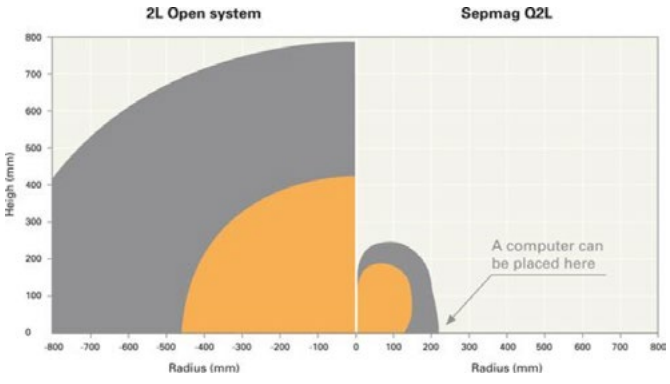
The use of magnetic systems always requires that two zones of safety be defined:

- **Caution area:** This is where the magnetic field B > 0.5 mT. In the caution area magnetic recording systems such as computers, credit cards and tapes as well as people with pace makers are banned.
- **Danger area:** This is where the magnetic field B > 3 mT. In the danger area, in order to avoid accidents, ferromagnetic tools are banned because they can be attracted by these strong stray fields. In addition, if several magnetic separators are used, their danger areas cannot intersect.

Unfortunately, space is costly and at a premium in the Life Sciences. If clean room facilities are needed, space is even more costly. Since this is the case, the aim should be to minimize the amount of space a system needs for its caution and danger areas.

Classic biomagnetic separators and magnet blocks have large stray fields due to the openness of their structure. The danger and caution areas increase as the size of the apparatus increase. But the size of the mandatory safety areas increase faster than the working volume, so more floor space is necessary for the danger and caution areas in order to comply with EHS regulations.

In contrast, the closed structure of homogenous biomagnetic separation systems such as SEPMAG systems, concentrates the magnetic energy in the working area with very minimal stray fields. The danger and caution areas are very small – a few centimeters or inches around the device – regardless of the size of the system. Several systems can be placed side by side and even computer can be placed in close proximity to these systems. Therefore in addition to the clear technical advantages of a homogenous biomagnetic separation system (e.g. no material losses, shorter separation time, easy resuspension, monitoring capability), these systems such as SEPMAG do not need large dedicated areas of the facility. This is highly cost effective and allows other production equipment to fit in the same area.



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