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Practical in-syringe mixing method for uniform particle delivery during embolization procedures

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Abstract

Embolic particles settle out of suspension inside syringes over time, leading to nonuniform particle delivery. A stepper motor stator was placed around a syringe containing a magnetic agitator to provide easily programmable rotating magnetic fields that result in the stirring of suspensions within the syringe. Injection uniformity was evaluated using a microscope, which recorded particle flow resulting from injections with and without mixing. Increasing delay times between initial uniform suspension and injection allowed particles to settle, which caused up to sixfold reductions in injection uniformity across all injection rates (1, 5, 10 mL/min), with particle boluses often ejected near the end of an injection. In-syringe mixing provided a fourfold improvement in injection uniformity at all injection flow rates following long delay times (120 s); at slow injection rates (1 mL/min), mixing provided better uniformity than all injections performed without mixing. Mixing performance was optimized by using moderate agitator rotation rates (~10 revolutions per second) and frequent changes in rotation direction (~every 250 ms). This compact solution for maintaining and injecting uniform embolic suspensions prevents particle settling, reduces variability during injections, and has applications in both clinical and research settings.

Keywords

Magnetic mixing, stepper motor, embolization, microspheres, syringe

Introduction

Particle embolization is a commonly used procedure for delivering highly localized treatment in a variety of clinical scenarios, ranging from vascular disorders to malignancies [1,2]. The embolic particles available for these procedures have diverse physical properties that can support different outcomes and typically come suspended in saline where they are negatively buoyant. Contrast agent is added to facilitate their visualization under x-ray fluoroscopic guidance and make the particles more neutrally buoyant, where additional preparation time is required to evenly suspend the particles before injection [3]. Even with adequate suspension, the particles settle to the bottom of the syringe over timeframes ranging from less than a minute to tens of minutes [3–6], depending on the type and size of particle, and the type and amount of contrast agent added. This settling necessitates frequent resuspension to ensure uniform delivery of the embolic material [7,8]. Since embolic particles are radiolucent, concentration changes due to particle settling typically go unnoticed during injection. Incorporating an in-syringe mixing mechanism could maintain uniform particle suspension throughout the injection, thereby removing the need for intermittent manual mixing and improving embolization uniformity.

Syringe mixers have been proposed for applications ranging from chemical synthesis and analysis [9–11] to keeping drugs or particles in suspension [12–14], using external magnetic fields. These solutions either rotate a magnet [11–13,15], rotate and translate a magnet [10,16], or utilize both gravity and a pulsed magnetic field [14] to move an agitator within the syringe. However, all these solutions are bulky, involve moving parts, and are not practical for use within an interventional setting, where the syringes are typically held and manipulated by the interventionalist.

In this study, we propose the use of a stator from a conventional stepper motor to apply a controllable rotating magnetic field within a syringe – without physically moving external components – in a manner that is compatible with various syringe sizes and models. Stepper motors are widely available and are used to produce precise rotation control of a rotor. A standard stepper motor contains a stator with eight poles that alternate phases. By removing the rotor, a syringe can fit through the stator bore. The stepper motor can then operate well below its step-rate limits as a magnetic agitator – introduced within the syringe – can have substantially fewer poles than the original rotor, making it a simple way of producing the magnetic fields necessary for mixing within a syringe.

The objective of this study was to develop and validate a practical method for mixing embolic particles within a syringe using a magnetic agitator driven by a stepper motor stator. We hypothesized that if the contents of a syringe are continually stirred, then embolic particles will be injected with uniform concentrations.

Materials and Methods

Magnetic mixing equipment

Magnetic field generation

To generate a rotating magnetic field within a syringe, a NEMA 8 bipolar stepper motor (WO-208-13-01-RO, Lin Engineering, California, USA) was disassembled to remove the rotor and shaft, exposing the stator (Figure 1a and Supplementary Video 1). With the rotor removed, a clear 12 mm diameter channel was available. The stator was driven by a micro-stepping stepper motor driver (TMC2208, Analog Devices, MA, USA), controlled by a dedicated microcontroller (Nano 33 BLE, Arduino, Monza, IT). Power for all components was supplied by four AA batteries. The motor driver was set to half-step resolution, allowing the magnetic field to transition more smoothly between adjacent stator poles. A full rotation of the stator's magnetic field consisted of 16 'steps,' each involving coordinated phase changes across the stator coils.

Magnetic agitators

The stator coil windings are designed with geometrically opposite coils that share the same polarity. Standard bar magnets cannot rotate smoothly in the stator bore because their poles prevent alignment with the stator's centerline. To enable mixing inside a syringe, custom magnetic agitators were designed to fit inside a syringe and spin in response to the rotating magnetic field generated by the stator positioned around the syringe.

Each magnetic agitator was designed to rotate about its center of mass by press-fitting two small Neodymium disk magnets (1.6 mm long, 1.5 mm diameter) into opposite sides of the agitator, as shown in Figure 1 (b,c). The magnets were oriented such that the same magnetic pole faced outward on both sides. Two designs were created: an impeller (Figure 1b) and a rod (Figure 1c), each with opposing holes to house the magnets. The magnetic agitators were 3D printed in poly-lactic acid (PLA) with a 0.05 mm Z-axis resolution (rather than the default of 0.2 mm).

[Figure 1]

Quantifying particle distribution

Embolic particles

To evaluate the uniformity of particle concentrations within injected suspensions, we studied a clinically used commercial hydrogel microsphere product (Bead Block, Biocompatibles UK Limited, Farnham, UK) with a nominal size range of 500–700 µm. The microsphere manufacturer specifies a slightly skewed particle-size distribution with a mean value of 550 µm (FWHM = 180 µm), and with over 90% of the particles falling within the nominal range. These microspheres were chosen for their large size, which makes flow behaviour easier to observe and increases settling speed compared to smaller particles.

The microspheres sink in water and float in contrast agent, so a mixture of the two liquids was required to make the microspheres roughly neutrally buoyant and increase their suspension time, following the instructions provided by the microsphere manufacturer. Suspension time was assessed by transferring the mixture to a standard 3 mL Luer-lock syringe (Medallion, Merit Medical Systems, South Jordan, UT), placing the syringe horizontally, and recording how long the particles remained suspended across more than two-thirds of the syringe volume [3]. Approximately 2 mL of deionized water and 2 mL of 370 mg I/mL contrast agent (Ultravist, Bayer, Mississauga, Canada) were first mixed with the microspheres and additional contrast agent (<0.2 ml) was added to the mixture until uniform suspensions could be maintained. The viscosity of this solution was estimated to be approximately 4 cP at 20 °C based on the contrast agent manufacturer data [17] and the exponential relationship viscosity has with concentration [18]. Resuspensions with the same liquid caused a change in buoyancy, potentially because some contrast agent diffused into the particles; this behaviour is likely representative of changes that would be observed in a clinical procedure. Equilibrium was reached after 10 mins, where the suspension time consistently remained at one minute. This mixture was used in all experiments for consistency.

Recording particle flow

To quantify the effects of various factors that affect particle concentration homogeneity at the exit of the syringe during injection, a custom 3D printed flow observation chamber was designed with a 5 x 22 mm channel covered by a watertight optical window created by melting and fusing clear plastic film (0.5 mm thick) onto the 3D printed component (Figure 2) using a soldering iron. The chamber, which was connected to the syringe via a Luer-lock connector, allowed particles to flow in near single-particle layers, minimizing superimposition.

Particle suspensions were injected into the chamber using a syringe pump (NE-8000, New Era Pump Systems, Farmingdale, NY) at constant flow rates (1, 5, 10 mL/min). The flow of particle suspensions was recorded through the optical window using a digital microscope (DM9H, Pepisky, China) at 25 frames per second, 1920x1080 resolution, with a 5 x 7 mm section of the flow channel in the field of view, which was illuminated using the white LEDs attached to the digital microscope.

[Figure 2]

Particle suspension states

To assess how the fraction of particles in suspension (floating vs settled) affects particle concentration uniformity during injection, particle mixtures were first fully suspended in a syringe and then injected under mixed and unmixed conditions through the flow observation chamber.

For injections without mixing, various delay times (0, 30, 60, 120 s) were introduced between suspension and injection to represent fully suspended, partially suspended, partially settled (particles occupying less than two-thirds of the syringe), and fully settled conditions. Each injection flow rate was tested at each time delay, with five replicates per condition.

For injections with in-syringe mixing, the mixing protocol shown in Figure 1d was followed (Supplementary Video 1a). A delay time of 120 s was introduced and during this delay, the magnetic agitator was rotated at a rotation rate (ω) of 10 revolutions per second (rps) with the direction of rotation reversing every three seconds. Mixing continued during each injection to test whether mixing could restore uniform particle flow under the least favourable condition where the particles would otherwise be fully settled.

To evaluate factors that alter the effectiveness of mixing, we varied the magnetic agitator parameters, including rotation rate (5, 10, 15 rps), and rotation phase duration (δ, time spent rotating before the direction reverses, 100, 250, 500, infinite ms). The parameters were analyzed with 5 mL/min flow, with three replicates per condition. Before each recorded injection, the particles were resuspended by rapidly transferring the mixture between two syringes at 15 mL/min three times using the syringe pump.

Video analysis

To compare the uniformity of particle concentration across different injection conditions, an in-house MATLAB script (R2024b, The MathWorks Inc., Natick, MA) was used to analyze recorded videos by counting the number of particles in each frame. The script identified all connected pixel regions and applied fixed area thresholds to differentiate between individual and overlapping particles. For each injection, the mean particle count across all frames was used as the reference value, representing a perfectly uniform injection. The deviation from the reference value was quantified using the normalized root mean square error (nRMSE) between the particle counts in each frame and the reference value. This metric highlights fluctuations in concentration, particularly cases with lower-than-average counts early in the injection and sharp increases near the end.

Statistical analysis

Statistical analysis was performed using GraphPad Prism10 (GraphPad Software, San Diego, CA). All nRMSE measurements were assessed for normality using the Shapiro-Wilk test. One-way analysis of variance (ANOVA) with post-hoc Tukey's honestly significant difference tests were used to identify all pairwise differences in nRMSE values between delay times, and also agitator design or usage. Two-way ANOVA was used to identify interactions between agitator rotation rate and rotation phase duration on nRMSE. Statistical significance was defined as $p \leq 0.05$.

Qualitative demonstration of mixing under diverse conditions

Settling time is inversely proportional to the density difference between the fluid and the particles, inversely proportional to the radius of the particles squared, and proportional to the viscosity of the fluid [19]. By varying the particle type or suspension fluid, a virtually unlimited number of experiments could be performed to characterize and optimize suspension and injection uniformity. To limit the complexity of this study while still demonstrating the range of the mixing method, the ability to mix embolic particles in diverse fluids inside a syringe was qualitatively assessed. The previously used 500–700 µm hydrogel particles were suspended in water alone to analyze the mixing performance in a fluid with a low viscosity (1 cP at 20 °C) and a lower density relative to the particles that caused the particles to rapidly settle. The particles were also suspended in 370 mg I/mL contrast agent to demonstrate the mixing performance in a fluid with a high viscosity (20.1 cP at 20 °C) and positive buoyancy, which caused the particles to float. In-syringe mixing (ω = 40 rps, δ = 1 s, interspersed with 2 s pauses) of embolic particles in these fluids was video recorded from an angle that could show the boundary between settled particles and the fluid.

Results

Effects of particle settling

We first evaluated how different stages of particle settling affect injection uniformity at different injection rates (Supplemental Video 2 (b,c)). Initially while particles were suspended, a moderate number of particles were expelled steadily from the syringe (Figure 3a). As delay times, or the time for each injection increased, more particles settled below the centerline of the syringe, causing a drop in particle expulsion during most of the injection (Figure 3b). Eventually, the syringe's rubber stopper piled the settled beads and forced them out in bulk, resulting in a sharp rise in particle expulsion at the end of the injection (Figure 3c).

[Figure 3]

The change in particle concentration throughout an injection with and without mixing is shown in Figure 4, which highlights times where few particles are ejected and times when particle boluses are ejected. The timing and intensity of particle boluses were influenced by both delay time and injection rate. At 1mL/min injection speeds, even with short delay times, particles fully settled mid-injection (Figure 4a). The slow injection speed also led to more variable particle release behaviour near the end of each injection (Figure 4b). In some instances, after a small initial particle bolus, only fluid was expelled near the end of the injection while leaving compacted beads in the syringe. In other cases, a second particle bolus occurred after a brief pause. In-syringe mixing had lower nRMSE values compared to all conditions without mixing.

The overall effects of settled particles on injection uniformity are shown in Figure 5. As expected, injection uniformity (lowest nRMSE) was highest when there was no mixing and no delay (i.e. injection immediately after suspension). Without mixing, each increase in delay time significantly increased the nRMSE at injection rates of 10 mL/min ($F(3,16) = 1084$, $p<0.001$) and 5 mL/min ($F(3, 16) = 270.3$, $p<0.001$). At 1 mL/min, all injections without mixing had nRMSE values above 0.8. At the longest delay, mixing with both a rod and impeller improved the uniformity (Supplemental Video 2a) at all injection rates (all $p<0.001$). However, the rod performed better than the impeller, showing lower and less variable nRMSE values and up to 10% higher average particle counts, so all other tests were done with the rod. When magnetic mixing with a rod was applied to 5 and 10 mL/min injections with the longest delay time, injection uniformity improved with a roughly fourfold reduction in nRMSE. At 1 mL/min injection uniformity improved with a twofold reduction in nRMSE compared to the best performing condition without mixing.

[Figure 4]

[Figure 5]

Optimizing mixing parameters

The impact of agitator rotation rates and rotation phase duration is demonstrated in Figure 6 for an injection rate of 5 mL/min. A two-way ANOVA revealed that both rotation rate and rotation phase duration significantly influenced nRMSE, $F(2,24) = 30.46$, $p<0.001$. The lowest nRMSE of 0.21 ± 0.02 was observed with $\omega = 10$ rps and $\delta = 250$ ms, which was about a 22% improvement from the non-optimized mixing protocol. Replicating this protocol at 1 mL/min produced an nRMSE of 0.28 ± 0.05. Low rotation rates around 5 rps have moderate nRMSE values above 0.3. Constant rotation direction and high rotation rates push particles away from the syringe outlet. Although high rotation rates following the protocol in Figure 1d produce poor results, the entire syringe volume could be resuspended compared to local mixing obtained with lower rates. Another mixing protocol (Supplementary Video 1b), where periodic high-speed mixing at 40 rps was interspersed with long pauses produced low nRMSE values around 0.2.

[Figure 6]

Mixing under diverse conditions

Supplementary Video 3 demonstrates the ability of in-syringe mixing to keep particles in suspension in diverse situations. Supplementary Video 3a shows that in a low viscosity fluid, in-syringe mixing can constantly and uniformly suspend all the particles in the syringe that would otherwise settle rapidly due to density differences with the fluid. Supplementary Video 3b shows that in a high viscosity fluid, in-syringe mixing can constantly and uniformly suspend a portion of particles, but a portion of the syringe volume opposite to the magnetic agitator was not influenced by the mixing.

Discussion

Sustained uniform suspension of embolic particles was achieved in this study by combining the stator from an off-the-shelf stepper motor and an in-syringe magnetic agitator. By using components from a conventional stepper motor to generate seamlessly controllable rotating magnetic fields we have demonstrated a practical solution with an optimized mixing protocol that can be applied during embolization procedures, as well as in all other circumstances where uniform suspension of particles needs to be injected, such as applications in microfluidics [14]. Matching the inner diameter of the stator to the syringe diameter ensures that the method can be applied across all syringe sizes and applications.

This method does not require any major modifications to preexisting equipment to generate the magnetic field, unlike other designs that require a modified syringe body [15], or specialized syringes designed for the mixing equipment [10,16]. Our method also does not have any critical restrictions for mixing functionality, unlike some designs that require gravity to work [14]. These advantages are particularly valuable in interventional settings, where clinicians can continue using techniques they are familiar with. Suboptimal particle suspension can lead to nonuniform particle concentration during injection, especially when there is a long delay between suspension and injection or when using slow injection rates. This phenomenon was particularly notable when particles have time to settle below the centerline of the non-mixed syringe due to delays or long injection times (Figure 4) in which case a greater proportion accumulates at the bottom of the syringe. A decrease in plunger speed appears to increase the tolerated density of the accumulated particles before the particles are pushed back up into the centerline to be ejected. Therefore, if particles begin to settle mid-injection, they can accumulate into a compressed mass of beads that are either not expelled at all if injection rates are too slow or are released as a sudden bolus. This can cause inconsistent dosing and may lead to lower-than-expected doses

In-syringe mixing was shown to recover particle concentration uniformity under conditions where particles would have fully settled otherwise. The rod-shaped magnetic agitator slightly outperformed the impeller design in achieving uniform particle injection, but both were found to perform well across diverse injection speeds. Therefore, in-syringe mixing can remove the trial and error required to produce uniform particle suspensions, obviating the need for precise manual preparation when otherwise suboptimal suspensions can be injected with uniform concentration when continually mixed.

The experiments demonstrated that not all mixing protocols performed equally well. There was less of a need to use optimized protocols at higher

(10 mL/min) injection rates compared to lower rates. Mixing rates should be fast enough to resuspend the particles near the agitator, but not fast enough to move particles laterally. Periodically reversing the rotation direction also prevented particles from being transported away from syringe outlet. This was evident from higher mean particle counts compared to conditions with constant rotation direction or excessively low or high agitator rotation rates. Excessively rapid reversals may also reduce performance as it may act as a barrier to particles exiting the syringe. However, intermittent short bursts of high-speed mixing can quickly resuspend the entire syringe volume without significantly disrupting the injection process. These bursts require less than half a second, which causes a brief dip in particle expulsion, but may be less disruptive overall for injections that take very long. This mixing protocol would likely be more resilient to syringe angle changes. Angled syringe orientations can result in particles accumulating due to gravity but is likely prevented if the entire syringe is resuspended, redistributing all particles uniformly across the syringe volume. However, this mixing method may be less robust to large variations in settling time, particularly samples with very quick settling times.

Particle settling rates and mixing performance are influenced by multiple variables, including particle size, relative density between the particle and fluid, viscosity of the fluid, syringe size [19], and stator size. While embolic particles are never suspended in water or concentrated contrast agent during clinical procedures, these extreme scenarios were used to qualitatively demonstrate that in-syringe mixing can prevent partial or complete particle settling even in extreme conditions. Mixing experiments in water alone demonstrated that the method is effective for negatively buoyant particles that settle rapidly, and suggesting the mixing method would be effective for dense particles, given they are small enough. This is the case for glass microspheres, which are the densest clinically used embolic particle type, but are only manufactured to have an average diameter of 25 µm, which limits their settling rate [20]. The demonstration of mixing in concentrated contrast agent showed that the viscosity of the fluid can impose limits on the effectiveness of the mixing method. While not relevant to embolization procedures, applications involving very viscous fluids will need more extensive optimization, including careful selection of a stepper motor / driver that possesses sufficient torque (typically provided by the motor manufacturer) [21,22]. It is important to note that both these viscosity changes may not fully represent the effects of changing the other suspension-related variables. Smaller particle sizes, tighter particle-size distributions, and increased particle-to-fluid ratios can result in the suspension exhibiting an increased viscosity and more pronounced non-Newtonian behaviour where shear forces (including from mixing) decrease the suspension viscosity [23, 24]. Suspensions with smaller particles and larger particle-to-fluid ratios also hinder settling effects where neighbouring particles increase fluid drag and reduce the overall settling rate [25], which may reduce the need for mixing. Therefore, there is a lot of potential variability in overall particle settling behaviour and mixing ability that can arise when changing suspension variables.

Overall, the quantitative experiments involving injections demonstrated that the act of resuspending particles either locally or throughout the syringe can provide significant improvements in injection uniformity. Combined with the qualitative results showing effective resuspension across diverse fluids, these findings show there is potential for in-syringe mixing to improve injection uniformity across different particle and suspension fluid combinations. This potential is especially strong in clinically settings, as embolic particles are often designed to have some degree of buoyancy in the intended suspension fluid [5, 8]. Although developing an optimal mixing protocol for specific particle, fluid, syringe size, and stator size combinations is beyond the scope of this paper and will need to be performed by future adopters, optimization may be streamlined by including adjustment knobs that change the rotation rate, rotation phase duration, and duration where rotation is paused, to fine-tune the mixing protocol to the suspension created. Mixing suspensions that exhibit non-Newtonian behaviour may require special attention, since shear thinning may make it more challenging to find the optimal mixing protocol.

Although embolization procedures are normally very safe, nonuniform injections may be less predictable and lead to serious clinical implications. For example, a large bolus of particles near the end of the syringe may be expelled abruptly, coinciding with the point where a target vessel is nearly occluded and lead to reflux and non-target embolization. A sudden delivery of a concentrated particle mass may also result in more proximal occlusion than intended, whereas a more uniform delivery would allow embolic material to reach distal vessels more predictably. Furthermore, particle accumulation in the syringe increases required injection pressure, which could falsely suggest a greater occlusion level at the target.

Limitations

The contrast-to-water ratio used in the experiments resulted in the particles settling quicker than values reported in literature [3]. In real-world settings, achieving perfectly tuned concentrations to maximize suspension time may not be practical, and variability between preparations is likely. In addition, the initial suspension in this study had a longer settling time than subsequent resuspensions, which is also likely to occur during lengthy procedures.

All injections were performed at constant flow rates, while the microsphere manufacturer suggests using slight pulsing action during injection. However, since our magnetic agitator is already next to the syringe outlet, variable injection speeds from hand injections would not prevent the agitator from following the stator's magnetic field; pulsing action imparted on the plunger by the user would ensure uniform suspensions in the syringe as it normally would, by agitating particles near the plunger.

In-syringe mixing was assessed with a syringe oriented horizontally through a single stepper motor stator model. Further testing is needed to assess how an inclined injection angle and choice of stator affect the ability to hold the agitator against gravity. Mixing would stop if the agitator exited the volume covered by the stator bore but can be easily resumed by lowering stator towards the fallen agitator and then repositioning it upward towards the syringe outlet. Stepper motors are produced in multiple sizes, with different lengths available for each frame (or stator bore) size. Longer stators or multiple stators in series would cover a greater volume in the syringe and reduce the chance the agitator falls out of the stator's magnetic influence, particularly during hand injections where the syringe angle may unintentionally change.

The entire syringe volume was also emptied all at once in our experiments. Prolonged embolization procedures using magnetic mixing may lead to heat generation in the syringe. The extent of heating and the mixing protocols that minimize it will need to be evaluated in the future. However, heating can be minimized simply by turning off the stator during anticipated delays; most stepper drivers (such as the TMC2208 used in this study) incorporate such an automatic standstill current reduction feature by default.

Lastly, the presence of the in-syringe agitator slightly reduces the usable volume in the syringe by some small proportion (0.25 mL in our case) dependant on the agitator thickness relative to the syringe diameter. However, this is unlikely to be a concern during embolization procedures where dose is not prescribed, but is instead determined by trial and error during the procedure since there is not a way to precisely predict how much embolic material is required to reduce blood flow to desired levels. This involves repeatedly refilling the syringe from a separate reservoir syringe, making it unnecessary to inject the entire syringe volume even without an agitator inside the syringe. Also, the agitators in this study were not made to be sterilized. Prior to clinical use, sterilization protocols will need to be developed. The magnetic agitators would need to be manufactured from materials that are compatible with clinical sterilization techniques and would likely be optimized for single use. Both limitations relating to the agitator can be easily remedied by manufacturing sterile syringes with embedded agitators that compensate for the lost volume.

Conclusions

Overall, this study demonstrates a simple and novel method of in-syringe mixing that can be achieved with readily available stepper motor stators and simple magnetic rods. This mixing mechanism can be easily implemented in clinical settings to help reduce embolization variability due to procedural oversights or imperfect particle suspension preparation. Syringe mixing can also be valuable in research settings where automated injectors are used, and particles cannot be resuspended easily after loading. Our versatile syringe mixing method has broad clinical and research applications in procedures that can be improved by ensuring that injections or suspensions are uniform.

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Author Contributions

DN: conceptualization, methodology, software, data collection and analysis, visualization, validation, original draft. MD: data analysis, visualization, supervision, review. DWH: conceptualization, methodology, data analysis, visualization, supervision, review.

Data availability

The data that support the findings of this current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare no competing interests.

Figure Captions

Figure 1. Syringe mixer components and temporal mixing protocol. CAD drawings show: (a) an exposed stepper motor stator with a syringe inserted through its bore and a rod-shaped magnetic agitator inside the syringe, (b) an impeller agitator with two opposing magnets, (c) a rod-shaped agitator with two opposing magnets. In each case the agitator rotates clockwise or anticlockwise when the stator is energized. Syringe mixing protocol (d) involves rotating the agitator at a rate, ω, for a rotation phase duration, δ, before reversing the rotation direction. The contents of the syringe are independently suspended before using the mixing protocol. There is typically a delay time between initial suspension and the start of an injection

Figure 2. Equipment for quantifying particle concentration uniformity. The exposed stepper motor stator generates a rotating magnetic field around the syringe placed in its bore, driving a magnetic agitator inside the syringe at controlled speeds using an Arduino Nano and a stepper motor driver. Injections are delivered at a constant rate by the syringe pump, with the flow passing an optical window in the flow observation chamber and recorded by a digital microscope.

Figure 3. Variation in particle concentration during injection. A time delay between particle suspension and injection causes the concentration to exhibit moderate density at the start (a), decrease as particles settle (b), and high concentration at the end as remaining particles are ejected in a bolus (c). The binary images (d, e, f) correspond to the coloured images above, with particles isolated from the background. Connected pixel areas were used to determine particle counts in each frame. The non-circular appearance of the beads is the result of a minor video camera artefact (rolling shutter).

Figure 4. Particle concentration (colour bars represent averages: top, standard deviations: bottom) throughout various injection conditions. Three injection rates were investigated: 1 mL/min (a, b), 5 mL/min (c, d), 10 mL/min (e, f). A 3-mL syringe was used for each injection where the injection duration was dependant on the injection rate. For each rate, six conditions were analyzed: four delay times between particle suspension and injection without mixing (NM), mixing with a magnetic impeller (IMP), and mixing with a rod-shaped (ROD) magnetic agitator. Delay times in seconds are indicated in the column labels. The magnetic agitators slightly reduced the usable syringe volume, indicated by the white spaces in the heatmaps.

Figure 5. Effect of mixing conditions on particle injection uniformity. Uniformity was measured using normalized root mean square error (nRMSE) of particle count per frame relative to the injection average. Non-mixing (NM) conditions included different delays between suspension and injection. Mixing

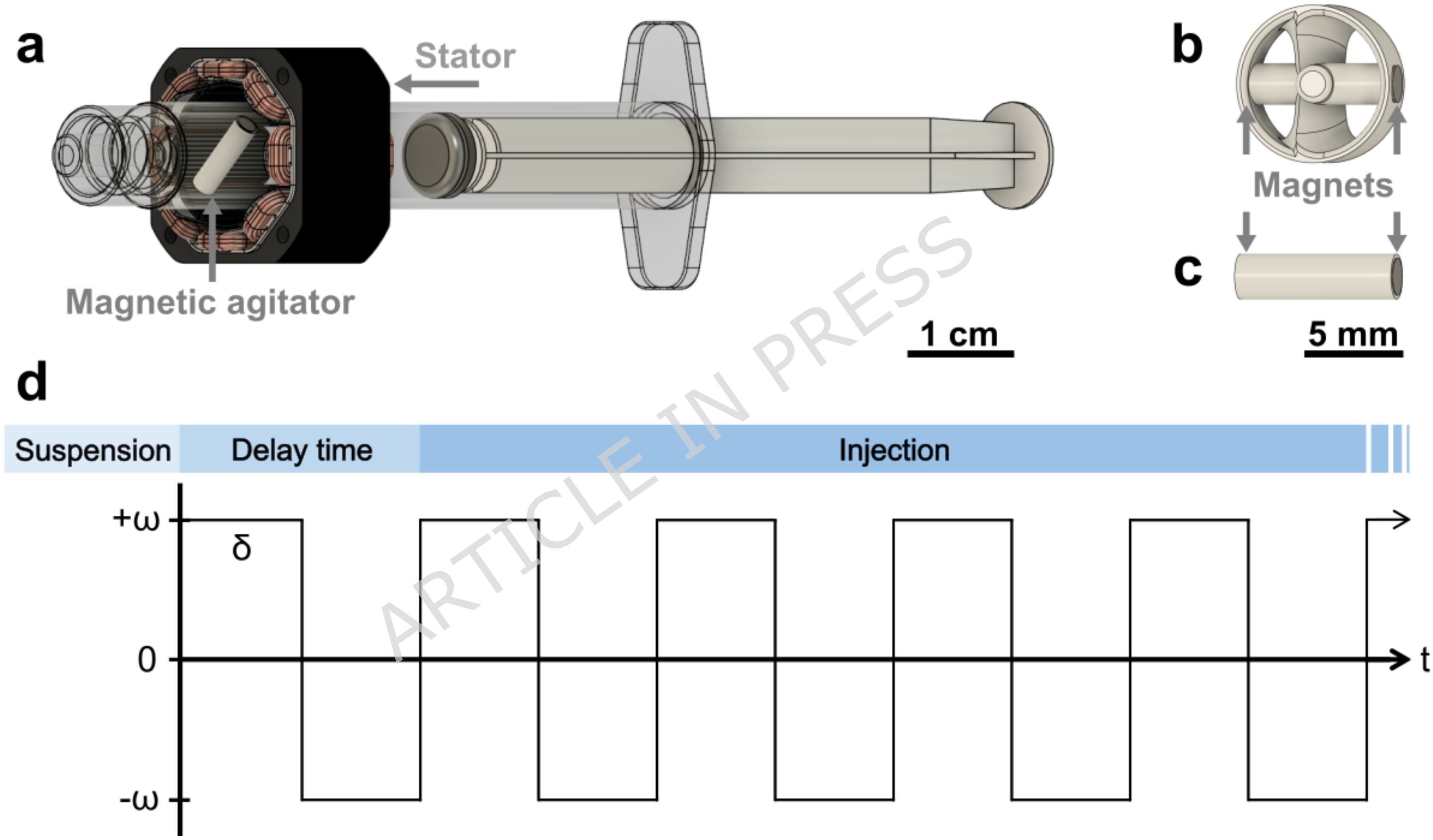
was performed with an impeller (IMP) or rod-shaped (ROD) magnetic agitator, with injection occurring 120 s after suspension. At a delay of 120 s, all nRMSE differences between unmixed and mixed conditions were statistically significant ($p<0.001$).

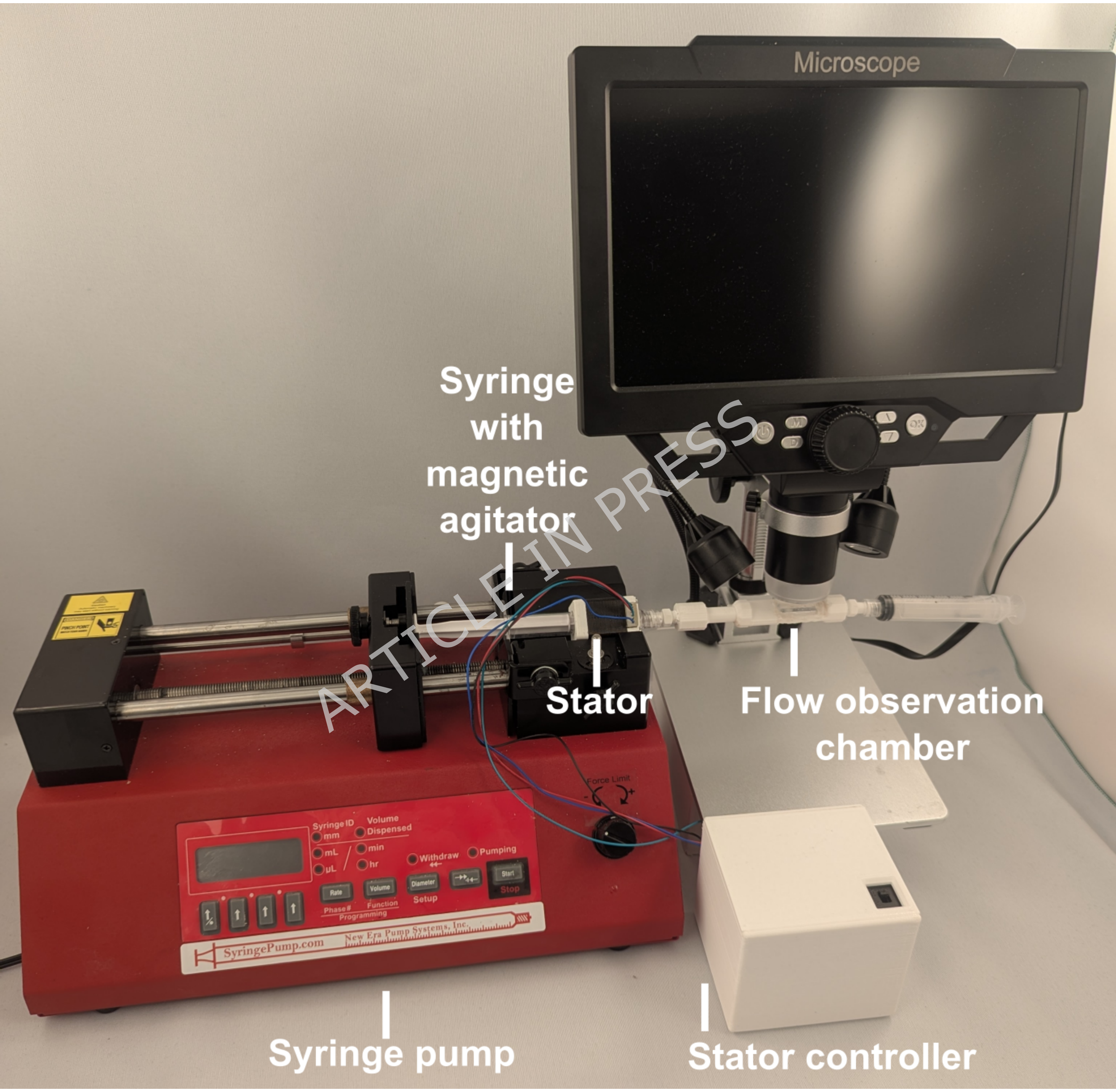
Figure 6. Effect of agitator rotation rate and rotation phase duration on particle injection uniformity. Each injection was performed at 5 mL/min. Uniformity was measured using normalized root mean square error (nRMSE) of particle count per frame relative to the injection average. Each group represents the agitator rotation rate, and each bar represents the duration before the rotation direction reverses. 'Infinite' indicates continuous rotation in a single direction (i.e. without reversal).

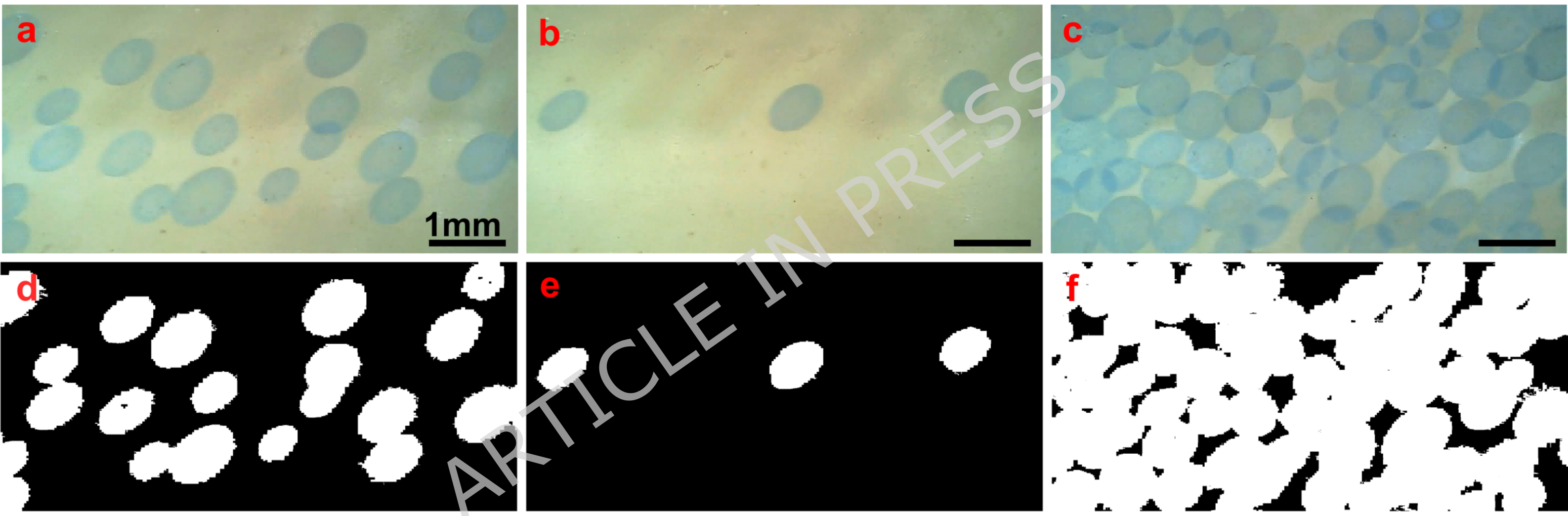
Supplementary Video 1: Visualization of the effectiveness of the stepper motor stator and magnetic agitator in producing uniform suspension of embolic particles within a 3 mL syringe. Mixing is performed with moderate-speed rotation with periodic changes in rotation direction (a), and high-speed mixing interspersed with pauses (b). The dot in the top right corner roughly indicates whether the stator is on (green) or off (white). The video demonstrated the ability of the agitator to stir the suspension as well as the severity of potential settling of particles when mixing stops near the end of the videos. In this demonstration, the beads are suspended in a solution with a lower concentration of contrast agent than the suspension used in the main analysis to exaggerate the settling effect.

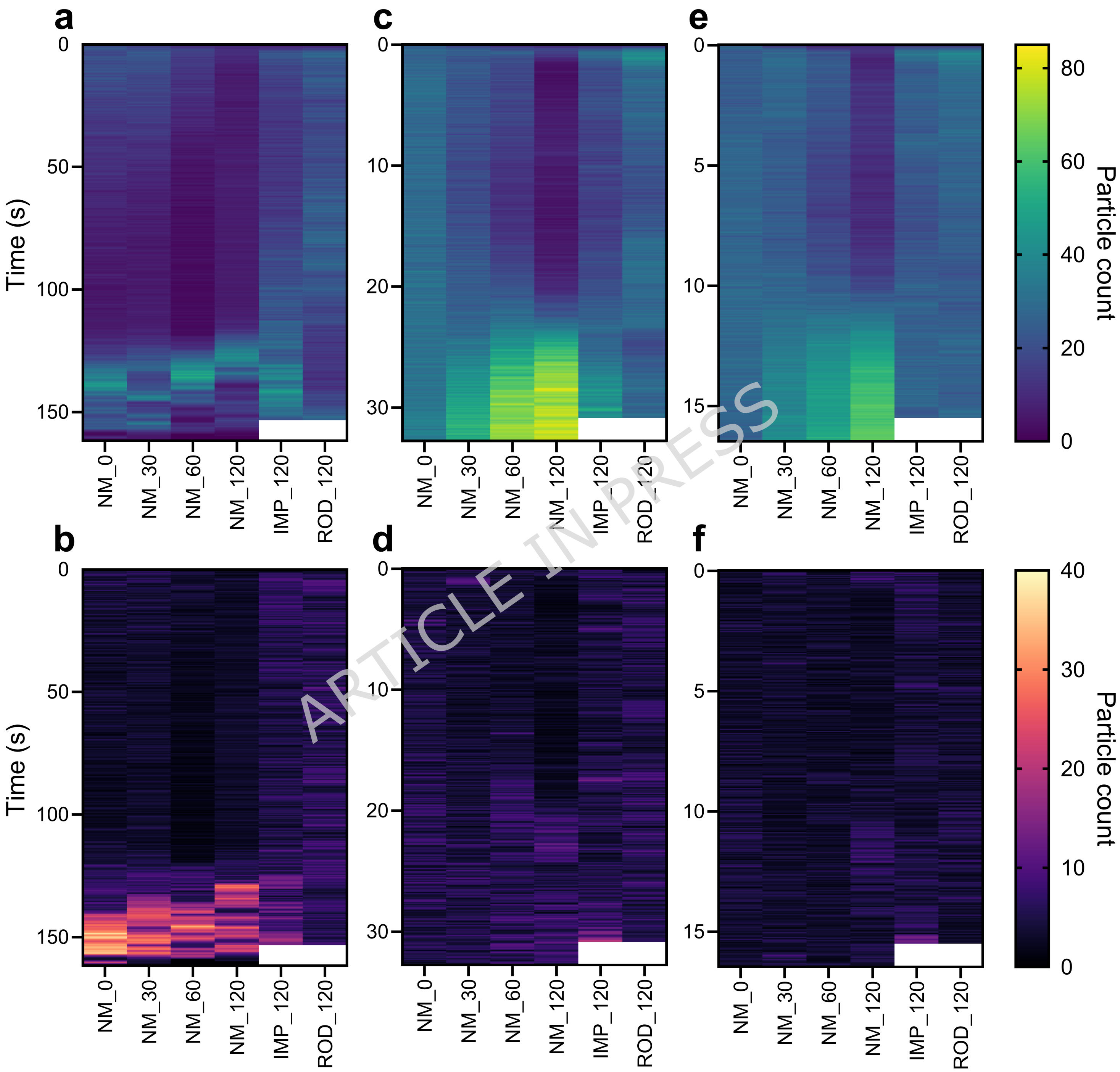
Supplementary Video 2: Visualization of the injection uniformity as particles are injected at 5 mL/min from a 3 mL syringe through the entrance of a three-way stopcock. Injections were performed with in-syringe mixing using a stepper motor stator and magnetic rod agitator (a), and without mixing, with injection starting immediately after uniform suspension (b), and two minutes after uniform suspension where the particles are fully settled (c). Each injection stopped with 0.25 mL of suspension left in the syringe to account for the volume taken up by the magnetic agitator. In this demonstration, the beads are suspended in a solution with a lower concentration of contrast agent than the suspension used in the main analysis to exaggerate the settling effect. Note that these videos were taken from above the syringe hence the effect of settling is not obvious in the syringe and can be perceived only in the stopcock.

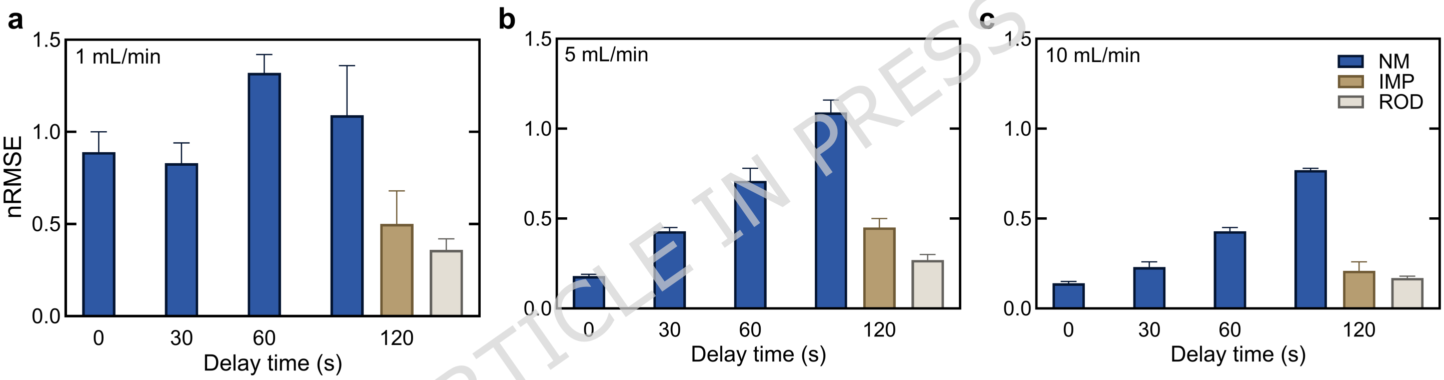
Supplementary Video 3: Effectiveness of the stepper motor stator and magnetic agitator in producing uniform suspension of embolic particles in different suspension fluids within a 3 mL syringe. Embolic particles suspended in water only (a) can be easily mixed despite the rapid particle settling rate due to the large embolic particle size suspended in a fluid with a large density difference compared to the particle. Embolic particles suspended in contrast agent only (b) cannot be uniformly resuspended throughout the syringe due to the viscous suspension fluid. Both mixing protocols used the same high-speed rotation rate interspersed with pauses. Note that these embolic particles are not designed to be suspended in only water or contrast agent, and this demonstration is only meant to explore the range of capabilities of this in-syringe mixing method with a stepper motor stator and a magnetic agitator in the syringe.


a
Stator
Magnetic agitator
1 cm
b
Magnets
c
5 mm
d
Suspension
Delay time
Injection
+ω
δ
0
t
-ω

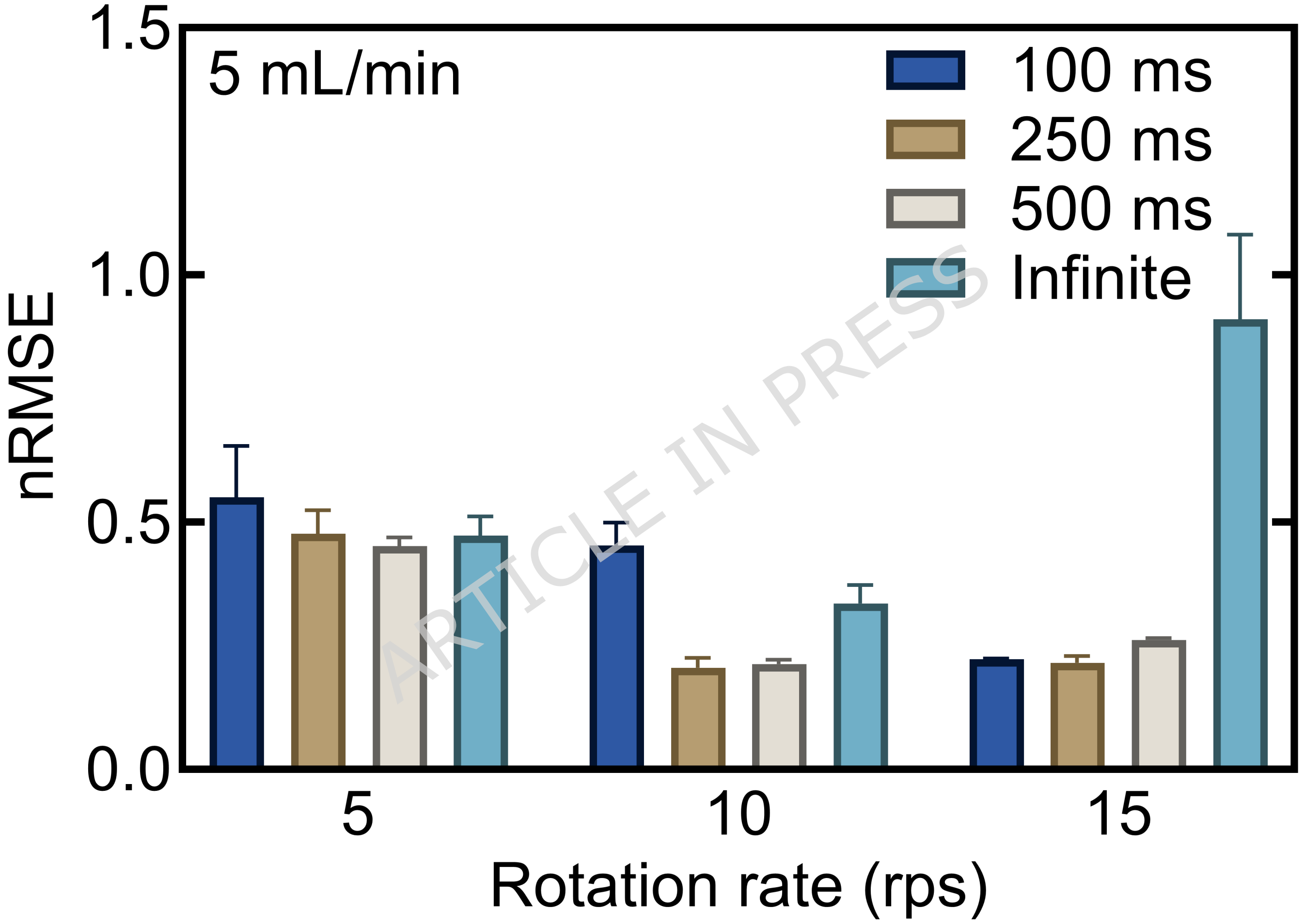

Microscope
Syringe with magnetic agitator
Stator
Flow observation chamber
Syringe pump
Stator controller


a
b
c
1mm
d
e
f


a
c
e
b
d
f
Time (s)
Particle count
NM_0
NM_30
NM_60
NM_120
IMP_120
ROD_120
0
50
100
150
0
10
20
30
0
5
10
15
0
20
40
60
80
0
10
20
30
40



a
1 mL/min
nRMSE
1.5
1.0
0.5
0.0
0
30
60
120
Delay time (s)
b
5 mL/min
1.5
1.0
0.5
0.0
0
30
60
120
Delay time (s)
c
10 mL/min
NM
IMP
ROD
1.5
1.0
0.5
0.0
0
30
60
120
Delay time (s)


1.5
1.0
0.5
0.0
nRMSE
5 mL/min
100 ms
250 ms
500 ms
Infinite
5
10
15
Rotation rate (rps)