JCAMECH

Vol. 51, No. 2, December 2020, pp 498-500
DOI: 10.22059/jcamech.2020.305072.524
Hypothesis

Are reported methods for synthesizing nanoparticles and microparticles by magnetic stirrer reproducible?

*Narges Mahmoodi[a], Jafar Ai[b], Zahra Hassannejad [c], Somayeh Ebrahimi-Barough [b], Elham Hasanzadeh [d], Amin Hadi [e], Houra Nekounam [f], and Vafa Rahimi-Movaghar [a],**

[a] *Sina Trauma and Surgery Research Center, Tehran University of Medical Sciences, Tehran, Iran*
[b] *Department of Tissue Engineering and Applied Cell Sciences, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran*
[c] *Pediatric Urology and Regenerative Medicine Research Center, Tehran University of Medical Sciences, Tehran, Iran*
[d] *Department of Tissue Engineering, School of Advanced Technologies in Medicine, Mazandaran University of Medical Sciences, Sari, Iran*
[e] *Cellular and Molecular Research Center, School of Medicine, Yasuj University of Medical Sciences, Yasuj, Iran*
[f] *Department of Medical Nanotechnology, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran*

ARTICLE INFO

Article history:
Received: 25 June 2020
Accepted: 02 September 2020

Keywords:
Vortex flow
Nanomedicine
Magnetic bar
Liquid height
Mono-dispersity

ABSTRACT

One of the most common tools for fabricating different drug-loaded polymeric particles is magnetic stirrer, a widely-used tool in nano-based drug delivery systems. Typically, the revolutions per minute (rpm) or G-Force of the stirrer are reported in related literature, while other parameters generate less attention and must be better understood. Reporting the rpm or G-Force is likely insufficient for producing the same vortex flow intensity and mono-dispersity as having a reliable and reproducible nanoparticle and microparticle synthesis method. We speculate that the magnetic stirrer bar's length and diameter, and the size of the cylindrical container, affect the qualities of nanoparticles and microparticles. Given the importance of these particle characteristics in the field of nanomedicine, understanding these details would improve reporting method reliability. These data are currently missing in most related papers and must be reported. The purpose of our study is to highlight the importance of these underestimated parameters (magnetic bar's length, diameter, and the size of the cylindrical container) and the impact on the reproducibility of particle synthesis methods using a magnetic stirrer.

1. Introduction

Nanomedicine is a multidisciplinary science that attracts researchers from different fields and viewpoints based on their academic backgrounds. It seems that despite the diversity of researchers, the importance of accurate reporting of some information is overlooked. Total transparency in reporting every aspect of experiments is necessary for having data reproducibility that allows others to thoroughly understand the steps the researchers took to achieve their results. Error and negligence in science may lead to gaps in knowledge and may unintentionally hinder research progress. Nanomedicine is a new emerging science that enables the delivery of drug release in a controlled manner at specific parts of the body [1].

In recent years, many studies have been published about the effects of different parameters on nanoparticle and microparticle characteristics in different synthesizing methods, including; single- or double emulsion, solvent evaporation, nanoprecipitation, ion gelation, and other similar approaches that require the use of a magnetic stirrer.

These fabricated particles have garnered attention for drug delivery applications, ranging from tumor therapy targeting to immune system modulation [2-5]. Also, the particles are more

* Corresponding author. Tel.: +98-216-675-7001; fax: +98-216-675-7009; v_rahimi@tums.ac.ir

efficient than using drugs individually for maintaining the half-life of drugs and reducing systemic side effects [6-8].

A recent study has pointed to the influence of different parameters on particle size and stability of nanoparticles [9]. However, despite the widespread use of magnetic stirrer for nanoparticles and microparticles synthesis, we have been unable to find parameters described in the experimental set up that affect the vortex flow, an important factor in providing a reproducible synthesizing method. Parameters such as the concentration of the involved materials, the order and volume of adding materials to the system, stir rate, time of stirring, temperature, and the total amount of the reaction are typically mentioned in articles [10-12].

Some parameters that affect fluid motion have generated less attention, including; the magnetic stir bar's length, diameter, and the exact shape, as well as the size of the cylindrical container (typically a beaker). The effects of the stir bar's parameters are more potent than the container's geometry. However, all these parameters affect vortex flow [13] and are essential for reporting. Although in recent years, researchers have begun publishing some of these parameters, [14-16] many still do not mention these measures in their writing. The reproducibility problems of nanoparticle and microparticle synthesis are mostly for mechanical stirring and need to be better understood [16].

2. Hypotheses

We hypothesize that the magnetic stir bar's length, diameter, and shape, and the size of the cylindrical container (beaker), affect the vortex flow intensity and mono-dispersity. These factors impact nanoparticle and microparticle size, distribution of size, drug loading capacity (LC), and encapsulation efficiency (EE). Thus, stating these parameters is essential for having reproducible results.

We propose that using a smaller magnetic bar, in general, will decrease the vortex flow intensity and mono-dispersity, and may increase particle size and distribution of size (Figure 1). Contrarily, using a larger magnetic bar would, therefore, increase vortex flow intensity and mono-dispersity, thereby decreasing particles size and their distribution size. Additionally, using a smaller beaker will increase the liquid height, reducing vortex flow intensity and mono-dispersity, especially at the surface. This may increase nanoparticle and microparticle size and their size distribution. Utilizing a larger beaker will, therefore, increase vortex flow intensity and mono-dispersity. Finally, the ratio of bar length to beaker diameter and the ratio of bar length to the height of the liquid in the filled beaker affects the vortex flow.

In general, reducing the liquid height in the beaker or increasing the magnet bar length and diameter may increase vortex flow intensity and mono-dispersion, leading to smaller and more uniform microparticles and nanoparticle sizes.

3. Evaluation of the hypotheses

It is necessary to experimentally study the effect of magnetic bar and beaker size on nanoparticle and microparticle size, drug LC, and EE of different polymers, drugs, and solvents. Nanoparticle and microparticle size can be measured by scanning electron microscope (SEM) and dynamic light scattering, while drug LC and EE can be evaluated by spectroscopy, nanodrop, high-performance liquid chromatography (HPLC) or liquid chromatography-mass spectrometry (LC-mas), depending on the amount of drug. Mathematical model design with mechanical engineering software would predict the exact relationship between different factors for vortex flow and synthesis of nanoparticles and microparticles.

4. Conclusion

In general, reporting routine equipment features in detail may seem trivial. However, it appears that most experiments are not entirely reproducible. The size of nanoparticles and microparticles has a tremendous impact on drug LC and EE and thus drug release. Accurate reporting of synthesis methods that result in reproducible particle size is therefore crucial for the field of nanomedicine to produce nanoparticles and microparticles with more controllable characteristics. Establishing an international guideline is necessary for writing reproducible methods of nanoparticle and microparticle synthesis. Such criteria would assist researchers in designing, conducting, and reporting experiments.

5. Acknowledgment

The authors want to thank Alexander R. Vaccaro and Paul Minetos for editing the manuscript.

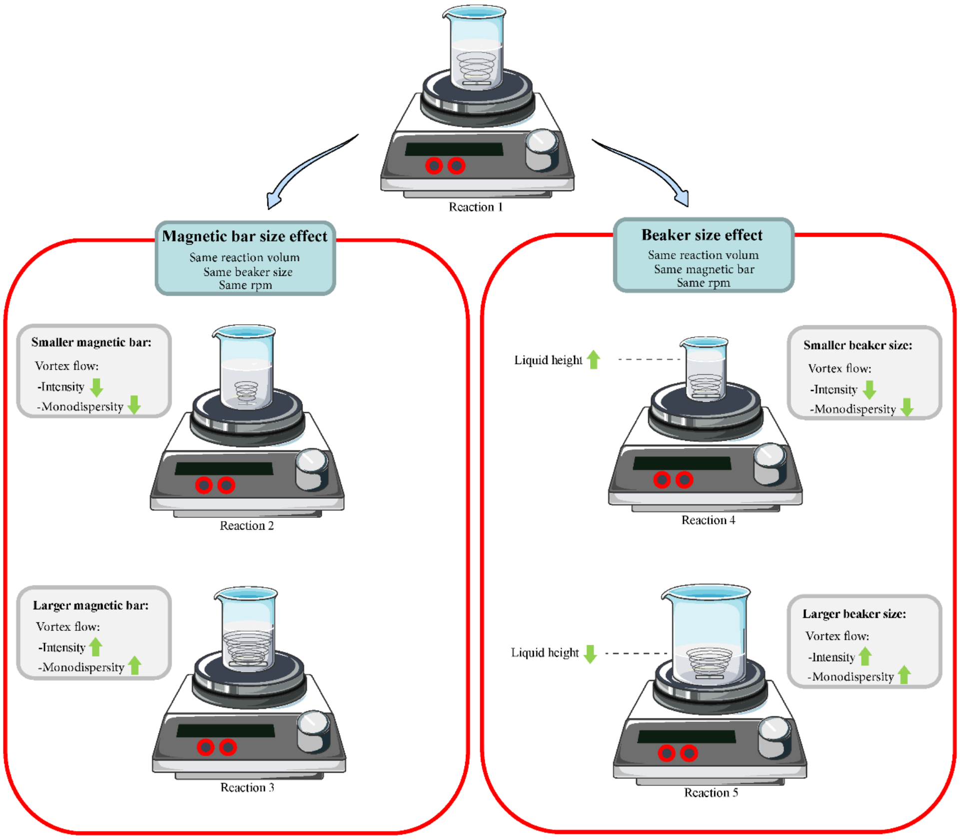

Figure 1. The probable effect of magnetic bar and beaker size on vortex flow, all in the same particle synthesis reaction volume.

References

1. Patra, J.K., et al., *Nano based drug delivery systems: recent developments and future prospects.* Journal of nanobiotechnology, 2018. **16**(1): p. 71.
2. Dang, Y. and J. Guan, *Nanoparticle-based Drug Delivery Systems for Cancer Therapy.* Smart Materials in Medicine, 2020.
3. Ben-Akiva, E., et al., *Polymeric micro-and nanoparticles for immune modulation.* Biomaterials science, 2019. **7**(1): p. 14-30.
4. Dacoba, T.G., et al. *Modulating the immune system through nanotechnology*. in *Seminars in immunology*. 2017. Elsevier.
5. Rezvantalab, S., et al., *PLGA-based nanoparticles in cancer treatment.* Frontiers in pharmacology, 2018. **9**: p. 1260.
6. Kızılbey, K., *Optimization of rutin-loaded PLGA nanoparticles synthesized by single-emulsion solvent evaporation method.* Acs Omega, 2019. **4**(1): p. 555-562.
7. Chenthamara, D., et al., *Therapeutic efficacy of nanoparticles and routes of administration.* Biomaterials Research, 2019. **23**(1): p. 1-29.
8. Onoue, S., S. Yamada, and H.-K. Chan, *Nanodrugs: pharmacokinetics and safety.* International Journal of Nanomedicine, 2014. **9**: p. 1025.
9. Hernández-Giottonini, K.Y., et al., *PLGA nanoparticle preparations by emulsification and nanoprecipitation techniques: effects of formulation parameters.* RSC Advances, 2020. **10**(8): p. 4218-4231.
10. Hawari, A., C. Tham, and Z.A.A. Hamid. *Effect of Synthesis Parameters on Size of the Biodegradable Poly (L-Lactide)(PLLA) Microspheres*. in *Advanced Materials Research*. 2014. Trans Tech Publ.
11. Jyothi, N.V.N., et al., *Microencapsulation techniques, factors influencing encapsulation efficiency.* Journal of microencapsulation, 2010. **27**(3): p. 187-197.
12. Aravand, M.A. and M.A. Semsarzadeh. *Particle formation by emulsion inversion method: effect of the stirring speed on inversion and formation of spherical particles*. in *Macromolecular symposia*. 2008. Wiley Online Library.
13. Halász, G., et al., *Vortex flow generated by a magnetic stirrer.* American Journal of Physics, 2007. **75**(12): p. 1092-1098.
14. McCall, R.L. and R.W. Sirianni, *PLGA nanoparticles formed by single-or double-emulsion with vitamin E-TPGS.* JoVE (Journal of Visualized Experiments), 2013(82): p. e51015.
15. Bile, J., et al., *The parameters influencing the morphology of poly (ε-caprolactone) microspheres and the resulting release of encapsulated drugs.* International journal of pharmaceutics, 2015. **494**(1): p. 152-166.
16. Li, D. and R.B. Kaner, *Shape and aggregation control of nanoparticles: not shaken, not stirred.* Journal of the American Chemical Society, 2006. **128**(3): p. 968-975.