JOURNAL OF CHEMICAL ENGINEERING AND INDUSTRIAL BIOTECHNOLOGY (JCEIB)
ISSN: 2600-7347 e-ISSN: 0126-8139
YEAR 2019, VOL. 05, ISSUE 02, 36 – 43
DOI: https://doi.org/10.15282/jceib.v5i2.3677

ORIGINAL ARTICLE

Effect of Surfactant, Solvent and Stirring Rate on the Synthesis of Silica Nanoparticles Entrapped Rifampicin

Junaidi Zakaria[1]*, Syamsul Rizal Abd Shukor[2], Khairunisak Abdul Razak[3]

[1]Faculty of Chemical and Process Engineering Technology, College of Engineering Technology, Universiti Malaysia Pahang, Lebihraya Tun Razak, 26300 Gambang, Kuantan, Pahang, Malaysia
[2]School of Chemical Engineering, Engineering Campus, Universiti Sains Malaysia, 14300 Seberang Prai Selatan, Pulau Pinang, Malaysia.
[3]School of Materials and Mineral Resources Engineering, Engineering Campus, Universiti Sains Malaysia, 14300 Seberang Prai Selatan, Pulau Pinang, Malaysia

ABSTRACT – In this study, silica nanoparticles entrapped with rifampicin has successfully been synthesized by using micelles entrapment approach. The goal of this study is to investigate the effects of synthesis parameters; surfactant (Tween 80), solvent (water) and stirring rate on the particles size and distribution of silica nanoparticles entrapped rifampicin. The results showed that without surfactant, larger mean particles (176.4 nm to 207.70 nm) of silica nanoparticles were produced while uniform and smaller spherical particles sizes (42.37 nm -70.44 nm) were formed with the addition of surfactant. But, when the amount of surfactant increased from 3.0 g to 9.0 g, larger silica nanoparticles with uniform size and thinner walls were observed until critical micelle concentration (CMC) of surfactant equivalent to 11.0 g was reached. The effect of water content shows the particle size slightly increased from 55.92 nm to 56.99 nm when the water content was increased from 150 mL to 200 mL, and decreased rapidly from 56.99 nm to 18.55 nm as the amount of water was increased from 200 mL to 350 mL. Meanwhile, for the effect of stirring rate, the mean particles sizes were recorded in the range of 39.11 to 80.15 nm. The largest size was observed at the lowest stirring rate (120 rpm) and the smallest size was observed at the highest stirring rate (520 rpm). The significant effect of these synthesis parameters can be used in developing a rational basis in tuning the size of silica nanoparticles for drug delivery system

KEYWORDS
Silica nanoparticles, Rifampicin, Surfactant, Solvent, Stirring rate.

INTRODUCTION

Recently, the advancement of nanoparticles with unique chemical and physical properties for drug delivery system (DDS) application has been well established. Previously, these DDS encounter serious limitations, such as high dose requirement, low bioavailability and off-target effects (Sen & Kettiger, 2018). The innovative use of nanoparticles has transformed the formulation and delivery of drug (Rizvi & Saleh, 2018). Nanoparticles are solid, colloidal particles with size range from 10 nm to 1000 nm; nevertheless, for nanomedical application, the preferential size is below than 200 nm (Biswas et al., 2014). It is prominent that the efficacy of most DDS is directly associated with particle size. Because of their small size and large surface area, drug nanoparticles have received more attention as they can be tailored for targeted delivery of drugs, improve bioavailability and provide a controlled release of drugs from a single dose (Zhang & Saltzman, 2013).

Numerous types of nanoparticles have been used as a carrier for DDS such as solid lipid nanoparticles (SLN), carbon nanotubes, polymeric nanoparticles, metal nanoparticles, ceramic nanoparticles and dendrimers, (Hughes, 2005; Arayne & Sultana, 2006; Abhilash, 2010). Among several DDS tested, silica nanoparticles have emerged as a new generation of inorganic platforms for biomedical application (Zhou, 2018). Silica nanoparticles have been highlighted because of its unique characteristics such as high mechanical strength, biocompatibility, resistance to microbial attack in a biological system and good chemical stability (Rosenholm et al., 2010). Besides, the precise structure of silica nanoparticles and the capability to change their surface have made them best candidates for DDS (Jisha et al., 2012, Wang et al., 2009). Other than that, most DDS are invented from silica due to the inexpensive cost and simple preparation. (Chen et al., 2012).

Many types of silica have been used for DDS such as silica aerogel, silica xerogel, core-shell silica, sol gel-based silica, mesoporous silica, and colloidal silica (Dorcheh & Abbasi, 2008; David et al., 2009; Finnie et al., 2009; Lu et al., 2010; Soyoung Lee et al., 2011; Tan et al., 2011). Usually, silica nanoparticles were synthesized from sol-gel process like Stober method, spray drying methods, sacrificial template and micelle formation approach (Bagwe et al., 2004; Ibrahim et al., 2010; Ge et al., 2009; Wab et al., 2012). Silica nanoparticles with controllable particle size and well-defined

*CORRESPONDING AUTHOR | Junaidi Zakaria | ✉ junaidibz@ump.edu.my

morphology can be prepared depending on the synthesis method. By applying these flexible functionalization methods, versatile silica nanoparticles are prepared and used as drug delivery agents through various mechanisms.

The properties of silica nanoparticles are affected by numerous synthesis parameters (Rahman et al., 2007). Therefore, in this work, the effects of synthesis parameters such as surfactant (Tween 80), solvent (water) and stirring rate on the particles size and distribution of silica nanoparticles was systematically studied. Most researches using poorly water soluble drugs like anti-inflammatory agents such as Ibuprofen and naproxen as drug model in the system. Thus, rifampicin, which is a poorly water soluble drug for tuberculosis was used as a drug model in this study. The micelles entrapment approach was used to synthesize the silica nanoparticles entrapped rifampicin. This approach has advantages of enhance drug solubility, prolong circulation half-life and possesses lower toxicity (Husseini & Pitt, 2008). The drug molecules are trapped temporarily inside silica matrix by physical means rather than chemical binding and easily dissociated because its electrostatic attraction between silica and drugs is weak (Vallet-Regi et al., 2001).

MATERIALS AND METHODS

Chemicals

Silica precursor (trimethoxyvinylsilane TMVS -98% pure), surfactant (Tween 80) and drug (Rifampicin) were purchased from Sigma-Aldrich Co. (MO, USA). Co-solvent (2-butanol-99 % pure) and 10 M ammonium hydroxide (31.5% NH_3 pure) were obtained from Fischer Scientific (Fairlawn, NJ). Solvent (deionized water) used in the study was generated by using Millipore filtration system (operating at 18.2 MΩ cm).

Preparation of silica nanoparticles

Micelles formation approach has been used to prepare the silica nanoparticles. Tween 80 was dissolved into 6 mL of 2-butanol, deionized water and ammonium hydroxide. Then, the solution was transferred into a 50 °C preheated bioreactor and then continuously stirred. Rifampicin drug and 2 mL of TMVS was further added into the preheated bioreactor and the medium was left overnight for 20 hours. The effect of Tween 80 (3.0 g- 11.0 g), water content (150 mL -350 mL) and stirring rate (120 rpm -520 rpm) on the particle size were investigated. Samples were characterized post dialysis process for five days.

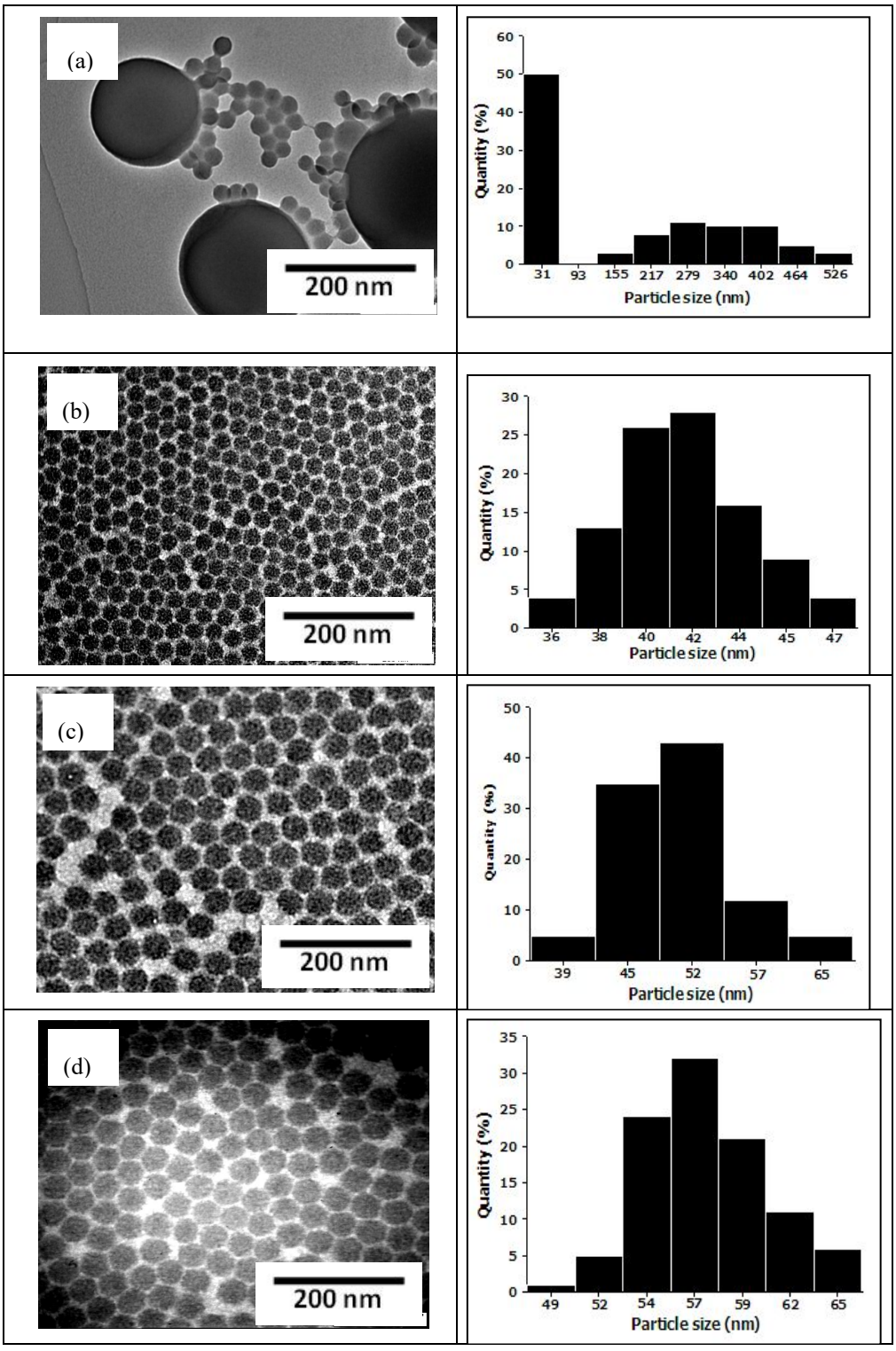
Analysis and characterization of silica nanoparticles

The hydrodynamic diameter of the silica nanoparticles was determined by dynamic light scattering (DLS) method using Zetasizer Nano ZS from Malvern Instrument. The particle size was analysed using a dilute suspension of nanoparticles in deionized water. The particle size represents the average size of silica nanoparticles. Transmission electron microscopy (TEM; Philips, model CM12, Eindhoven, Netherlands- operated at 120 kV) has been used capture the images of the silica nanoparticles. A droplet of silica nanoparticles sample has been transferred on a carbon-coated copper grid for TEM observation. The sample was allowed to dry for three minutes at room temperature. Then, the grid is observed with TEM without being stained. The images were taken at a number of random positions on the grid. ImageJ Version 1.43 software has been used to measure the diameter of nanoparticles. The size of the nanoparticles was calculated from the TEM images using an average of 100 particles for all samples.

EXPERIMENTAL RESULTS

Effect of surfactant (Tween 80)

Effects of surfactant to the particle size distribution of silica nanoparticles entrapped rifampicin are shown in Figure 1(a)- (f). From Figure 1(a), it can be seen that without the addition of surfactant, non-uniform and bimodal particle size distribution with large and small size of silica nanoparticles has been produced. However, when the amount of amount of surfactant was added with increment from 3.00 g to 9.00 g, the particle size distribution was also increased from 42.37 nm to 70.44 nm as can be observed from Figure 1(b)-(e). This condition revealed the formation of thinner walls and large uniform size of silica nanoparticles with the addition of surfactant. The addition of surfactants increases the size because the adsorbed surfactant layer has provided a hydrophobic microenvironment at the silica surface and thus led to the formation of a stable micelle structure (Wang et al., 2007). The micelles began to form when surfactant reaching critical micelles concentration (CMC). The CMC is the minimum amount of surfactant required to form micelles (Owena et al., 2012). Unfortunately, Figure 1(f) shows that the particle size decreased at 11.0 g of surfactant. This suggested at this point the amount of surfactant surpasses the optimum amount needed for the formation of silica nanoparticles, so the viscosity of the aqueous solution reduced and formed small spheres as supported by Chen et al., (2010).


(a)
200 nm
Quantity (%)
Particle size (nm)
31 93 155 217 279 340 402 464 526
(b)
200 nm
Quantity (%)
Particle size (nm)
36 38 40 42 44 45 47
(c)
200 nm
Quantity (%)
Particle size (nm)
39 45 52 57 65
(d)
200 nm
Quantity (%)
Particle size (nm)
49 52 54 57 59 62 65

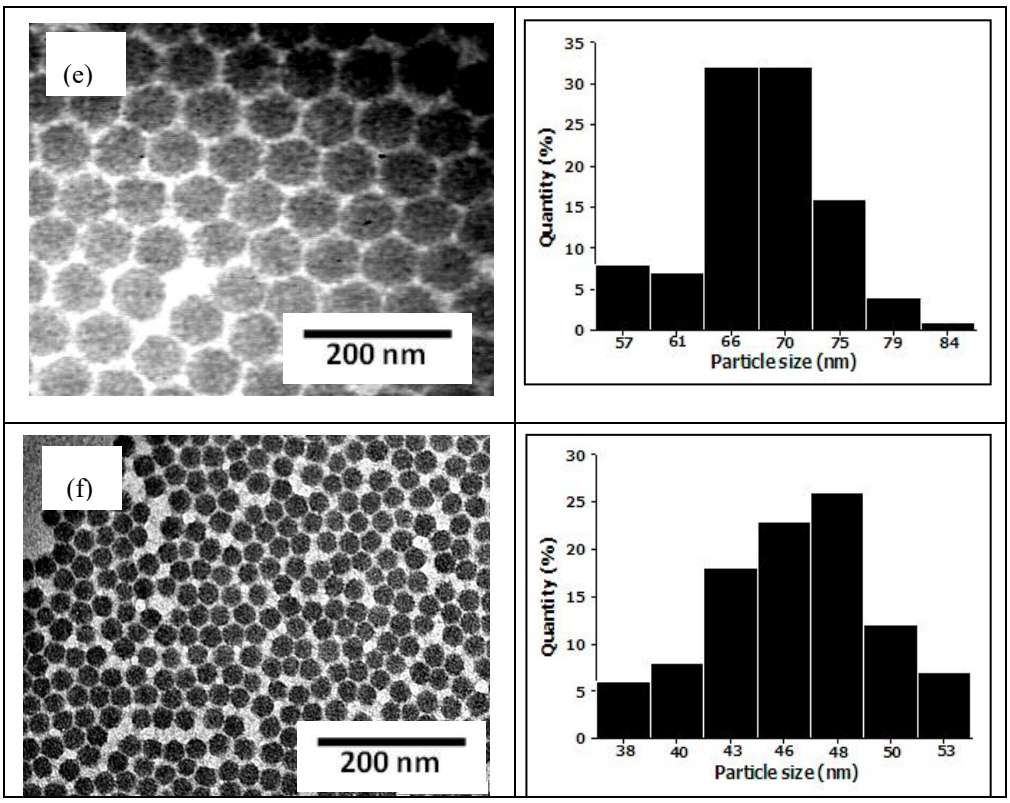
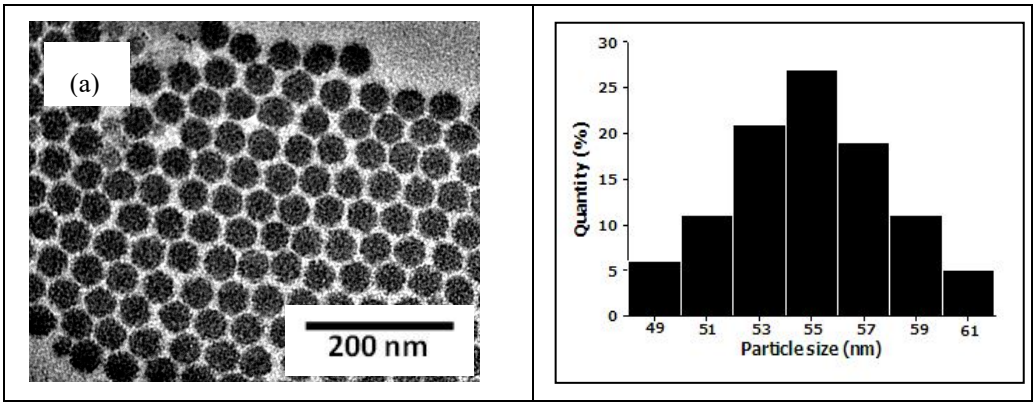


Figure 1. TEM images and histograms of particle size distribution of silica nanoparticles entrapped rifampicin at different amount of Tween 80: (a) 0 g, (b) 3.0 g, (c) 5.5 g, (d) 7.0 g, (e) 9.0 g and (f) 11.0 g

Effect of solvent (water content)

Hydrolysis of silica precursor is a prolonged reaction; thus catalysts are needed to increase the rate of reaction. In this study, ammonium hydroxide (NH_4OH) is used as a catalyst to enhance the hydrolysis and condensation of silica precursor in an alcoholic medium. NH_4OH was added to ensure the pH is maintained in the range of 9 to 11. Besides the catalyst, water also plays an important role as a solvent in this process. In order to study the effect of water content on the size of synthesized particles, the amount of water was varied from 150 mL to 350 mL and the other variables were kept constant. The results of the effects are shown in Figure 2 (a-e). The particle size slightly increased from 55.92 nm to 56.99 nm when the water content increased from 150 mL to 200 mL. Surprisingly, the particle size decreased rapidly from 56.99 nm to 18.55 nm as the amount of water is increased from 200 mL to 350 mL. This is in agreement with the finding from by Rao et al. (2005) as it is revealed that high amount of water encourages high nucleation rate and consequently led to the formation of smaller-sized silica particles



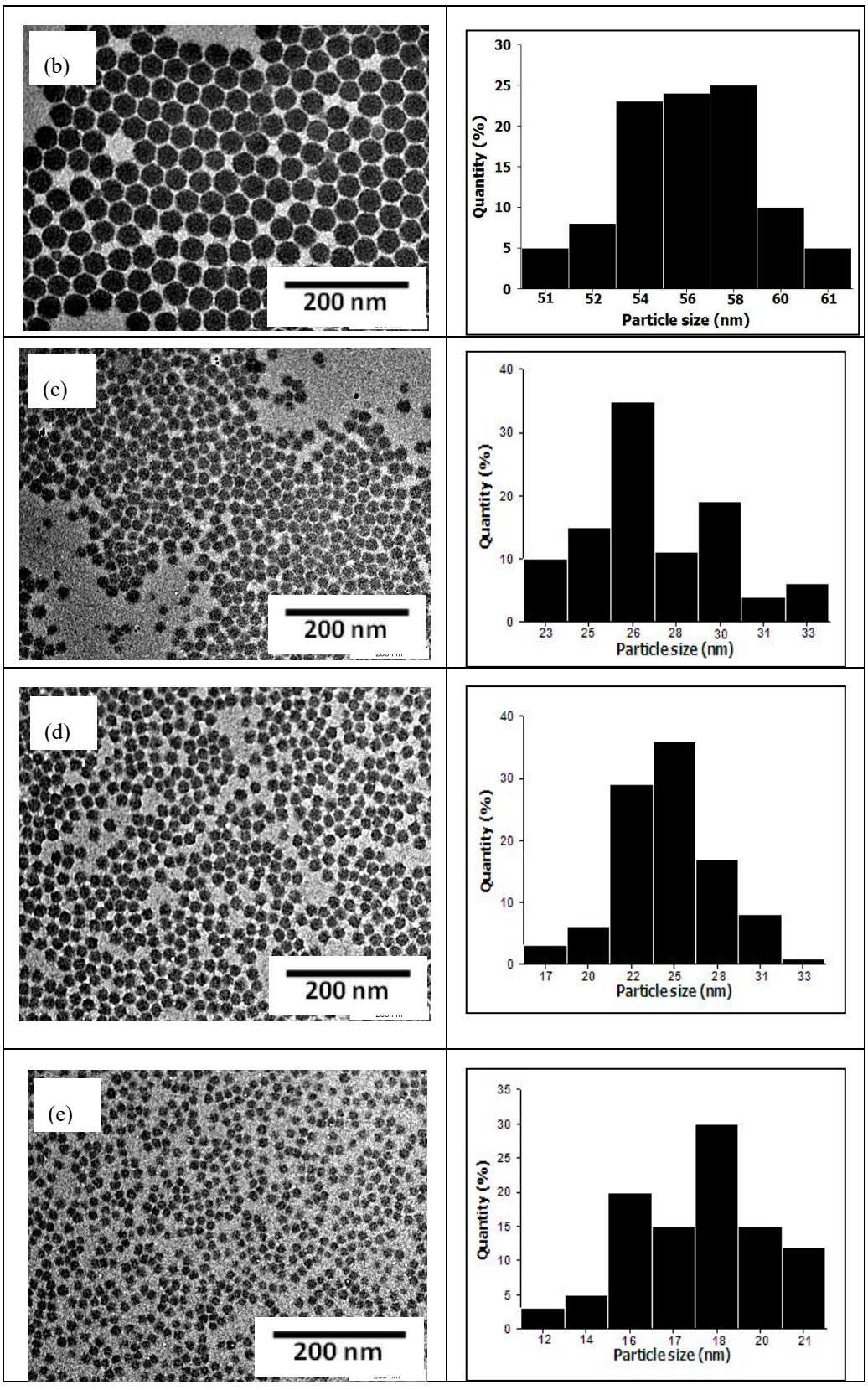
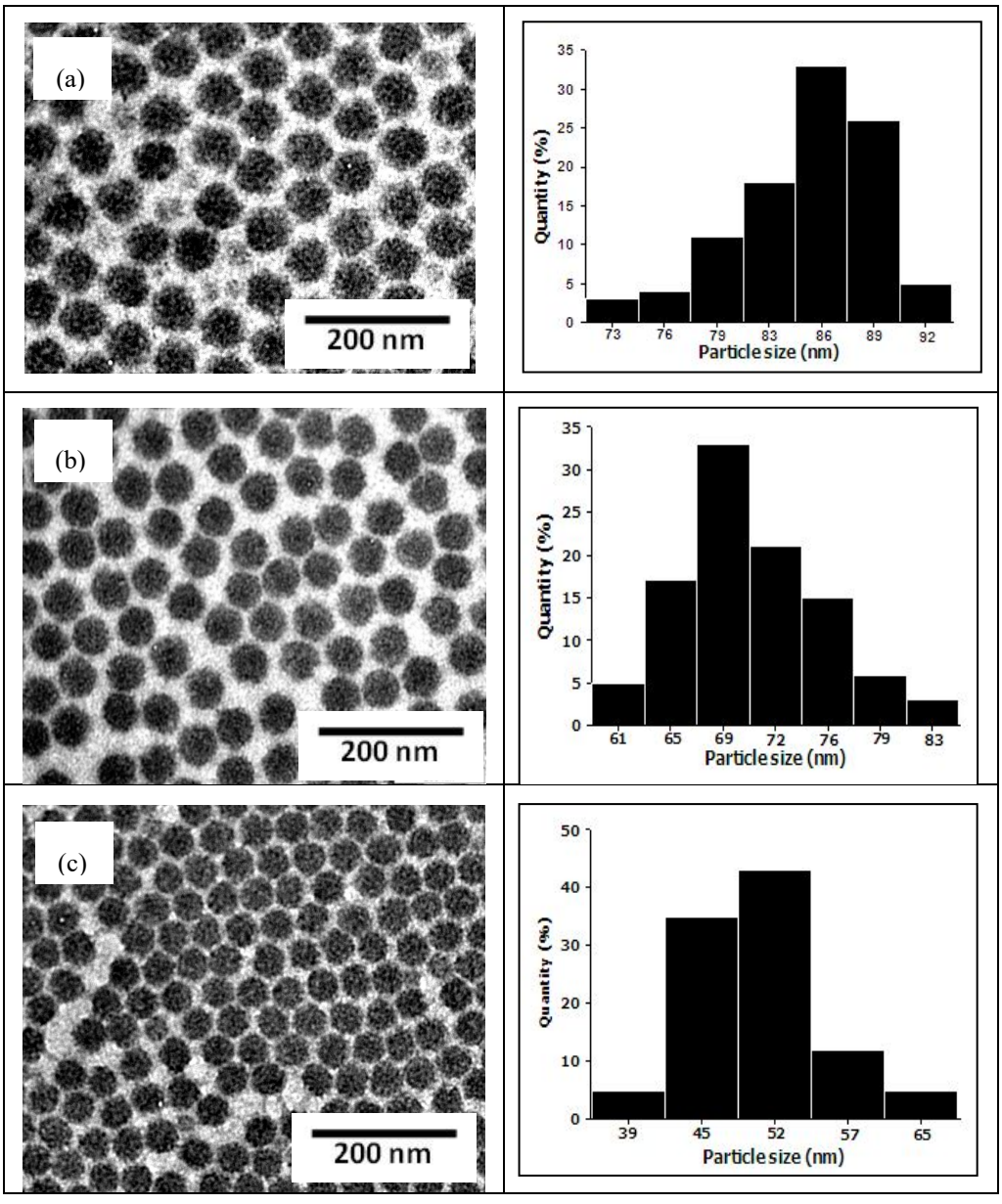


Figure 2. TEM images and histograms of particle size distribution of silica nanoparticles entrapped rifampicin at different volume of water: (a) 150 mL, (b) 200 mL, (c) 250 mL, (d) 300 mL and (e) 350 mL

Effect of stirring rate

Figure 3 (a-e) shows the effect of stirring rate to particle size distribution of the silica nanoparticles entrapped rifampicin. The stirring rates were varied from 120 rpm to 520 rpm by adjusting the digital stirrer at the reactor vessel. From all the figures, it can be seen that the particle size decreased with the increased of stirring rate. When the stirring rate increased from 120-520 rpm, the particles decreased from 80.15 nm to 39.11 nm as shown in Figure 3 (a-e). Furthermore, at higher stirring rate, the structures of the particles were found not to be in well spherical shape and bimodal distribution. These findings suggested that higher stirring rate enriches the hydrolysis rate of silica precursor, producing more silica particles at the initial stage of the reaction while lower stirring rate may hinder the hydrolysis of silica precursor in the emulsion system and led to formation of larger particle size (Yokoi et al., 2009). Similar findings have been observed by Zawrah et al. (2009).



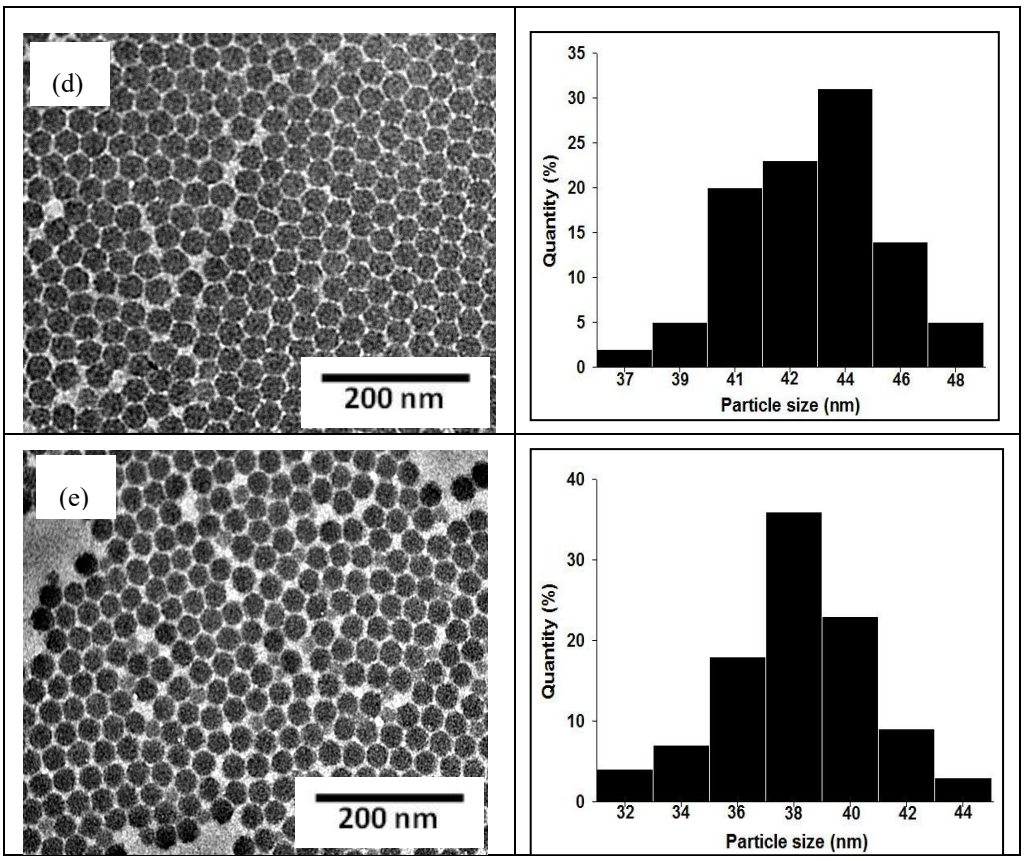


Figure 3. TEM images and histograms of particle size distribution of silica nanoparticles entrapped rifampicin at different stirring rate: (a) 120 rpm, (b) 220 rpm, (c) 320 rpm, (d) 420 rpm and (e) 520 rpm

CONCLUSION

In this study, various sizes of spherical silica nanoparticles entrapped rifampicin were successfully produced by using the micelle formation approach. The results showed that without surfactant, larger mean particles (176.4 nm to 207.70 nm) of silica nanoparticles were produced while uniform and smaller spherical particles sizes (42.37 nm -70.44 nm) were formed with the addition of surfactant. But, when the amount of surfactant increased from 3.0 g to 9.0 g, larger silica nanoparticles with uniform size and thinner walls were observed until critical micelle concentration (CMC) of surfactant equivalent to 11.0 g was reached. The effect of water content shows the particle size slightly increased from 55.92 nm to 56.99 nm when the water content was increased from 150 mL to 200 mL, and decreased rapidly from 56.99 nm to 18.55 nm as the amount of water was increased from 200 mL to 350 mL. Meanwhile, for the effect of stirring rate, the mean particles sizes were recorded in the range of 39.11 to 80.15 nm. The largest size was observed at the lowest stirring rate (120 rpm) and the smallest size was observed at the highest stirring rate (520 rpm). To conclude, within the scope of this study, the results demonstrated that particles size and distribution of the silica nanoparticles entrapped rifampicin is highly dependent on the surfactant (Tween 80), solvent (water content) and stirring rate. These results can be used in developing a rational basis to tune the size of silica nanoparticles in order to be used as a drug carrier system.

ACKNOWLEDGMENT

The author would like to appreciate the financial supports from Universiti Malaysia Pahang through Research Grant Scheme, RDU1703316 and also School of Chemical Engineering and Institute for Research in Molecular Medicine (INFORMM), Universiti Sains Malaysia (USM) through Research University Cluster Grant (1001/PSF/861001).

REFERENCES

Abhilash, M. (2010). Potential applications of nanoparticles. *International Journal of Pharma and Bio Sciences,* 1, 1-12.

Arayne, M. S. & Sultana, N. (2006). Nanoparticles in drug delivery for the treatment of cancer. *Pak. J. Pharm. Sci.,* 19, 256-258.

Bagwe, R. P., Yang, C., Hilliard, L. R. & Tan, W. (2004). Optimization of dye-doped silica nanoparticles prepared using a reverse microemulsion method. *Langmuir,* 20, 8336-8342. https://doi.org/10.1021/la049137j

Biswas, A.K., Islam, M.R (2014). Nanotechnology based approaches in cancer therapeutics. *Adv. Nat. Sci.: Nanosci. Nanotechnol.* 5,

043001. https://doi.org/10.1088/2043-6262/5/4/043001
Chen, Q., Han, L., Gao, C. & Che, S. (2010). Synthesis of monodispersed mesoporous silica spheres (MMSSs) with controlled particle size using gemini surfactant. *Microporous and Mesoporous Materials,* 128, 203–212. https://doi.org /10.1016/j.micromeso.2009.08.024.
Chen, Q., Larismaa, J., Anu, K.-H., Vilonen, K., Soderberg, O. & Hannula, S.-P. (2012). Effect of synthesis time on morphology of hollow porous silica miicrospheres. *Materials Science (Medziagotyra),* 18, 66-71. https://doi.org/10.5755/j01.ms.18.1.1344
David, Q.-G., Adriana, G.-Q., María, G. N.-A. & Elizabeth, P.-S. (2009). Silica xerogels as pharmaceutical drug carriers. *Expert Opinion on Drug Delivery,* 6, 485-498
Dorcheh, A. S. & Abbasi, M. H. (2008). Silica aerogel: Synthesis, properties and characterization. *Journal of Materials Processing Technology,* 199, 10–26. https://doi.org/10.1517/17425240902902307
Finnie, K. S., Waller, D. J., Perret, F. L., Krause-Heuer, A. M., Lin, H. Q., Hanna, J. V. & Barbe, C. J. (2009). Biodegradability of sol-gel silica microparticles for drug delivery. *J Sol-Gel Sci Technol,* 49, 12-18. https://doi.org/10.1007/s10971-008-1847-4
Ge, C., Zhang, D., Wang, A., Yin, H., Ren, M. & Liu, Y. (2009). Synthesis of porous hollow silica spheres using polystyrene–methylacrylic acid latex template at different temperatures. *Journal of Physics and Chemistry of Solids,* 70, 1432–1437. https://doi.org/10.1016/j.jpcs.2009.08.013
Hughes, G. A. (2005). Nanostructure-mediated drug delivery. *Nanomedicine: Nanotechnology, Biology, and Medicine,* 1, 22 – 30. https://doi.org/10.1016/j.nano.2004.11.009
Husseini, G. A., & Pitt, W. G. (2008). Micelles and nanoparticles for ultrasonic drug and gene delivery. *Advanced Drug Delivery Reviews*, 60(10), 1137–1152. https://doi.org/10.1016/j.addr.2008.03.008
Ibrahim, I. A. M., Zikry, A. A. F. & Sharaf, M. A. (2010). Preparation of spherical silica nanoparticles: Stober silica. *Journal of American Science,* 6, 985-989.
Jisha, E. R., Balamurugan, G., Selvakumar, P., Edison, N. & Rathiga, R. (2012). Synthesis of silica nanoparticle by chemical method and their antibacterial activity. *International Journal of PharmTech Research,* 4, 1323-1331.
Lu, J., Liong, M., Li, Z., Zink, J. I. & Tamanoi, F. (2010). Biocompatibility, biodistribution, and drug-delivery efficiency of mesoporous silica nanoparticles for cancer therapy in animals. *Small,* 6, 1794-1805. https://doi.org/10.1002/smll.201000538
Owena, S. C., Chana, D. P. Y. & Shoichet, M. S. (2012). Polymeric micelle stability. *Nano Today,* 7, 53–65. https://doi.org/10.1016/j.nantod.2012.01.002
Rahman, I. A. (2007). An Optimized Sol-Gel Synthesis of Stable Primary Equivalent Silica Particles. *Colloids and Surfaces A: Physicochemical and Engineering Aspects,* 294(1–3), 102–10. https://doi.org/10.1016/j.colsurfa.2006.08.001
Rao, K. S., El-Hami, K., Kodaki, T., Matsushige, K. & Makino, K. (2005). A novel method for synthesis of silica nanoparticles. *Journal of Colloid and Interface Science,* 289, 125-131.
Rizvi, S. A. A. and Saleh, A. M. (2018). Applications of nanoparticle systems in drug delivery technology. *Saudi Pharmaceutical Journal. King Saud University,* 26(1), 64–70. https://doi.org/10.1016/j.jsps.2017.10.012
Rosenholm, J. M., Sahlgren, C. & Linden, M. (2010). Towards multifunctional, targeted drug delivery systems using mesoporous silica nanoparticles - opportunities & challenges. *Nanoscale,* 2, 1870-1883. https://doi.org/10.1039/c0nr00156b
Sen, D. and Kettiger, H. (2018). Silica-based nanoparticles as drug delivery systems: *Chances and challenges 1.* https://doi.org/10.1016/B978-0-12-813661-4.00001-8
Soyoung, L., Hui-Suk, Y. B., & Kim, S.-H. (2011). The comparative effects of mesoporous silica nanoparticles and colloidal silica on inflammation and apoptosis. *Biomaterials,* 32, 9434-9443. https://doi.org/10.1016/j.biomaterials.2011.08.042
Tan, S., Wu, Q., Wang, J., Wang, Y., Liu, X., Sui, K., Deng, X., Wang, H. & Wu, M. (2011). Dynamic self-assembly synthesis and controlled release as drug vehicles of porous hollow silica nanoparticles. *Microporous and Mesoporous Materials,* 142, 601–608. https://doi.org/10.1016/j.micromeso.2011.01.004
Vallet-Regi, M., Rámila, A., del Real, R. P., & Pérez-Pariente, J. (2001). A New Property of MCM-41: Drug Delivery System. *Chemistry of Materials*, 13(2), 308–311. https://doi.org/10.1021/cm0011559
Wab, H. A. A., Zakaria, N. D., Aziz, A. A. & Razak, K. A. (2012). Properties of amorphous silica entrapped isoniazid drug delivery system. *Advanced Materials Research,* 364, 134-138. https://doi.org/10.4028/www.scientific.net/AMR.364.134
Wang, W., Gu, B. & Liang, L. (2007). Effect of anionic surfactants on synthesis and self-assembly of silica colloidal nanoparticles. *Journal of Colloid and Interface Science,* 313, 169–173. https://doi.org/10.1016/j.jcis.2007.04.042
Wang, X., Liu, L.-H., Ramström, O. & Yan, M. (2009). Engineering nanomaterial surfaces for biomedical applications. *Experimental Biology and Medicine,* 234, 1128-1139. https://doi.org/10.3181/0904-MR-134
Yokoi, T., Wakabayashi, J., Otsuka, Y., Fan, W., Iwama, M., Watanabe, R., Aramaki, K., Shimojima, A. & Tatsumi, T. (2009). Mechanism of formation of uniform-size silica nanospheres catalyzed by basic amino acids. *Chemistry of Materials,* 21, 3719–3729. https://doi.org/10.1021/cm900993b
Zawrah, M. F., El-Kheshen, A. A. & Abd-El-Aal, H. M. (2009). Facile and economic synthesis of silica nanoparticles. *Journal of Ovonic Research,* 5, 129-132.
Zhang, J. and Saltzman, M. (2013). Engineering biodegradable nanoparticles for drug and gene delivery. *Chem. Eng. Prog.,* 109 (3), 25–30.
Zhou, Y. (2018). Mesoporous silica nanoparticles for drug and gene delivery. *Acta Pharmaceutica Sinica B. Elsevier B.V.,* 8(2), 165–177. https://doi.org/10.1016/j.apsb.2018.01.00