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Various Chloride Salt Addition in Mesoporous Material (SBA-15) Synthesis and Potential as Carrier for Dissolution Enhancer

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ABSTRACT
Nano pores in Santa Barbara Amorphous (SBA-15) has potential to be employed as a carrier to enhance solubility and dissolution. Addition of salt on surfactant solution enabling the SBA-15 synthesis process carried on room temperature instead of 35-50˚C. Atorvastatin Ca, which belongs to Biopharmaceuticals Classification System (BCS) class II, has low solubility in water, was used as a model drug. SBA-15 was synthetized using Pluronic P123:H2O:HCl:TEOS on 0.02:166:6:1 molar proportion with addition of 6 moles of inorganic salts: NaCl, KCl, $MgCl_2$, and $CaCl_2$. SBA-15 was impregnated to drug solution in methanol with SBA-15:ATV proportion of 1:1 before it was evaporated. The unloaded and loaded mesoporous were characterized with DTA, pXRD, FT-IR, BET and SEM. The result showed the highest surface area achieved by $MgCl_2$ addition as 724.227 m^2/g, meanwhile the biggest pore size and pore volume achieved was by the addition of KCl as 5.411 nm and 8,948 x 10^{-1} cm^3/g. The dissolved amount in phosphate buffer 0.05 M pH 6.8 showed the significance enhancement by 2.5 to 6-fold at 5 min in comparison with intact atorvastatin Ca. In conclusion, the properties of SBA-15 vary with the addition of different salts, and can be used to enhance the dissolution of atorvastatin Ca.

Keywords: *Mesoporous material, SBA-15, atorvastatin Ca, dissolution*

1. INTRODUCTION

Dissolution is the process by which the active substance in a dosage form released and dissolved in the media dissolution in the form of molecules [1]. According to Noyes-Whitney equation, dissolution rate of a drug depends on the value of the drug's solubility [2–4]. With enough permeability, drug that rapidly dissolved would be quickly absorbed. So, for the low solubility substances, the dissolution process would be the rate limiting steps for absorption and would affect the onset of pharmacological effects. More than 40% of drug compounds that have been developed have a low solubility in water due to the modifications are aimed to obtain a better permeability and be in harmony with the Biopharmaceuticals Classification System (BCS), these drugs would be classified as the BCS class II [5].

Several methods to improve the solubility of the compound have been developed, such as the decrease of particle size, solid dispersion, use of β-cyclodextrin, modification of the shape of the crystal, solid lipid nanoparticles and drug delivery system in the form of a colloid [5–8]. In addition to these methods, mesopores materials that have pores within nanoscales had potential as carrier to improve the drug dissolution rate by expanding the surface contact between the active substances with the dissolution media [9–14]. In other hand, the nanoscale pore can be utilized to inhibit the process of crystal growth [15]. Theoretically, particles in the form of amorphous will give a better solubility than the crystal.

SBA-15 (Santa Barbara Amorphous) synthesized using triblock-copolymer surfactant which in the solution will form the conformation of the micelles. The micelles are then coated with silica from the hydrolysis of the precursor silica tetraethyl ortho-silicate (TEOS) [16]. NaCl addition in the synthesis of SBA-15 affected the nature of the pores of SBA-15. Pore size increased due to

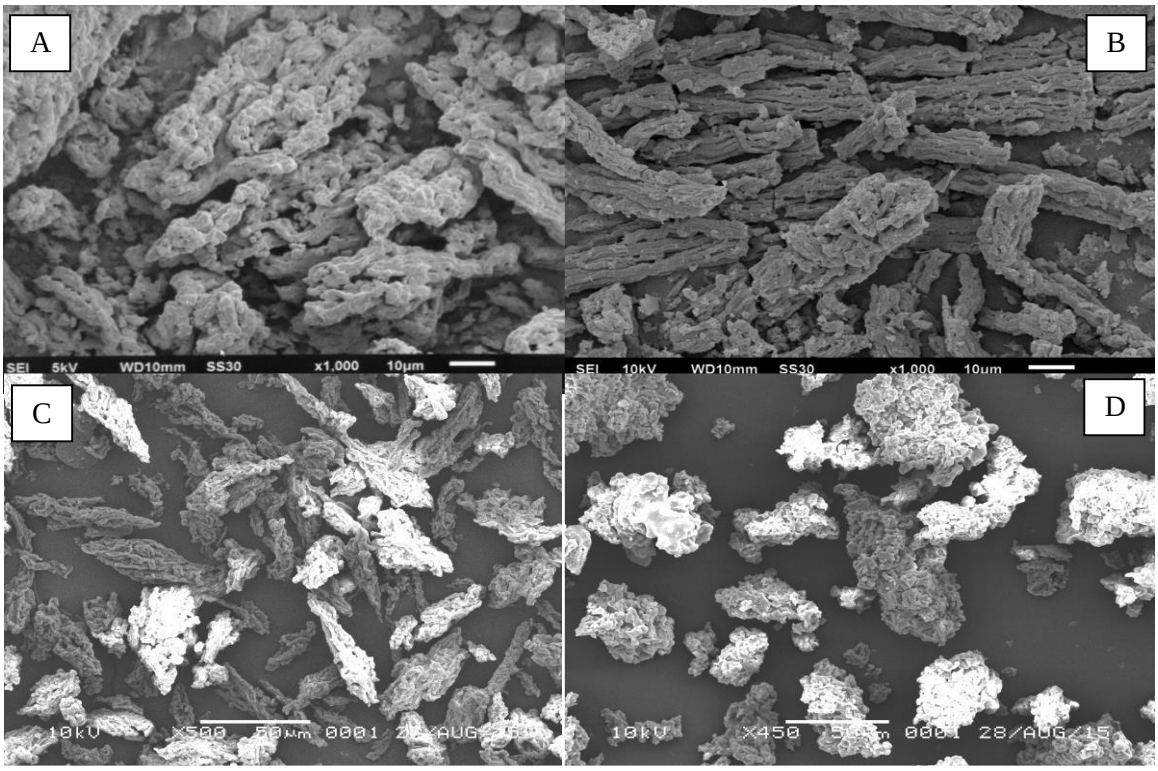

Figure 1 SEM images of SBA-15 synthesized with addition of 6 moles: NaCl (A), KCl (B), $CaCl_2$ (C) and $MgCl_2$ (D)

the presence of salt in the surfactant solution, it shows similar effects with the increasing of the formation temperature. In addition, the use of salt can expand the possibilities of the synthesis conditions, such as temperature and concentration of surfactant used, as well as allowing the use of surfactants to produce an uniform mesostructured pores [17,18]. This research aims to study how the influence of differences in the type of salt used on the characteristics of SBA-15 is produced, and the ability of SBA-15 to improve the dissolution of drug ingredients using atorvastatin Ca as a model..

2. METHODS

Mesoporous SBA-15 were synthesized using Pluronic P123 (Sigma Aldrich) as triblock copolymer templates, and tetraethylorthosilicate (TEOS) (Sigma Aldrich) as the silica precursor in HCl media. Four solution of Pluronic P123 in 2 M HCl solution were each stirred at 300 rpm in room temperature with addition of NaCl, KCl, $CaCl_2$ or $MgCl_2$ for 24 hours. After the micelles were formed, the silica precursor added dropwise under vigorous stirring (700 rpm) for 3 hours. According to Yu et,al research at 2001, the molar ratio of TEOS:HCl:H_2O:P123 was 1:6:166:0.02 with addition of 6 moles of inorganic chloride salts. As for hydrothermal process, the solution was stored at 80ºC for 24 hours. The white gel-like precipitate were vacuum filtered and washed thoroughly with distilled water before dried at 50ºC overnight. To remove the surfactant template, the white powder was calcinated in 550ºC furnace for 4 hours.

The SBA-15 powders were characterized for powder X-ray diffraction (XRD) pattern using Bruker D8 Advance. The morphological image was obtained using JEOL T330A. BET analysis was carried out with Quantachrome-Nova 3200e to determine the pore size, surface area, pore volumes and isotherm adsorption curves.

Atorvastatin Ca (Teva-tech) in methanol with concentration of 5 mg/ml were used to impregnate the unloaded SBA-15 (1:1 weight ratio) under stirring at 300

Table 1 Pore properties of synthesized SBA-15

Parameters	NaCl-SBA	KCl-SBA	$MgCl_2$-SBA	$CaCl_2$-SBA
Pore volume (x10^{-1} cm^3/g)	7.205	4.280	7.844	6.005
Pore diameter (nm)	5.0194	5.4211	4.3325	3.6346
Surface area (m^2/g)	574.168	311.988	724.227	660.850

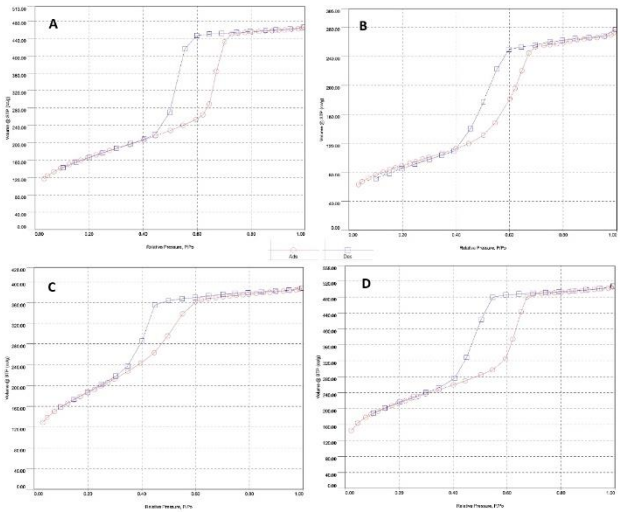

Figure 2 Isotherm curves of NaCl-SBA-15 (A), KCl-SBA-15 (B), $CaCl_2$-SBA-15 (C), and $MgCl_2$-SBA-15 (D)

rpm and heated at 80ºC until the mixture dried. The amorphous atorvastatin Ca was obtained by the same technique. The loaded SBA-15 was subjected for complete analysis of SEM (JEOL T330A), fourier transform infrared (FT/IR-4200 Type A), differential thermal analysis (Linseis STA PT 1600), and powder X-ray diffraction (Bruker D8 Advance).

The dissolution test was carried in 900 ml 0.05 M phosphate buffer pH 6.8. The dissolution tester (Hanson research SR8Plus) with paddle was set for 75 rpm, 37ºC ± 0.5°C for 2 hours. The sample of intact atorvastatin Ca, amorphous atorvastatin Ca and SBA-loaded equal to 20 mg of atorvastatin Ca were used in the dissolution test. The amount atorvastatin Ca dissolved were determined with spectrophotometer UV at 240 nm.

3. RESULTS AND DISCUSSION

Various morphological shape of SBA-15 was successfully synthesized by the addition of several chloride salts. A well-ordered fiber particles were found by addition of 6 moles of KCl (Figure 1.B), meanwhile the addition of NaCl given a less ordered fiberlike particles (Figure1.A). The other chloride salts addition constructs a short flakes and inhomogeneous mesoporous particles (Figure 1.C and D). Kubo in 2007 discussed the effect of synthesis parameters such as temperature, times, and addition of inorganic salts to the morphology of synthesized mesoporous silica SBA-15. Apparently all three factors affect the product. The stirring temperature affect the morphology and meso/microstructure of SBA-15. A normal stirring temperature was between 40-45ºC would results a long fiberlike particles, meanwhile a higher or lower temperature would lead to short and inhomogeneous particles as result [19]. The morphological looks of mesoporous material were the result of the template shape, in this topic would relate to the Critical Micelle Concentration (CMC) of the surfactant. The CMC shape would depends on the surfactant concentration and solution condition as temperatures or presents of salts. There are three region of temperature during the micelle formation: unimer region (low temperature) where the methyl groups of PPO become hydrated and formed hydrogen bonds with water from the media; CMT (Critical Micelle Temperature) when the methyl groups rotate and the hydrogen bonds are broken are called transition region; and micelle region where all the surfactants aggregated in micelle form since the interaction PPO-water reduced and turn into PPO-PPO interaction [20]. Salt addition would affect the CMT and sphere to rod transition of micelle by increasing or decreasing the number of hydrogens bonded -OH groups. Most of the anion presence affect the polymer solubility and the salting out strength follow the Hofmeister series, meanwhile Cl^- only has minor effect on water structure [20,21]. The morphology of multivalent cation salts added SBA-15 as inhomogeneous flakes (Figure 1.C and D) is the result of incomplete sphere-to-rod transition process.

Chloride salts used in this research can be grouped by the cations as monovalent and bivalent cation and by the anions amount. Based on the pore properties listed in Table 1, the monovalent cations existence in micellar solution yields a larger pore size compared to bivalent cations. Denkova was previously explained that multivalent cations are likely to have a greater salting-out power [21]. The greater salting-out power would dehydrate the PPO groups and lead to the breakage of the hydrogen bonds, and PPO groups would attract to each other and formed a smaller micelle spheres and rods. The effect of anion amount added to the surfactant solution would be explained by comparing the pore volume and surface area of NaCl-SBA with $MgCl_2$-SBA and KCl-SBA and $CaCl_2$-SBA. It was found that the later have a slightly larger pore volume and the BET surface area increased from 574.168 to 724.227 m^2/g and from 311.988 to 660.850 m^2/g. It is interesting that both

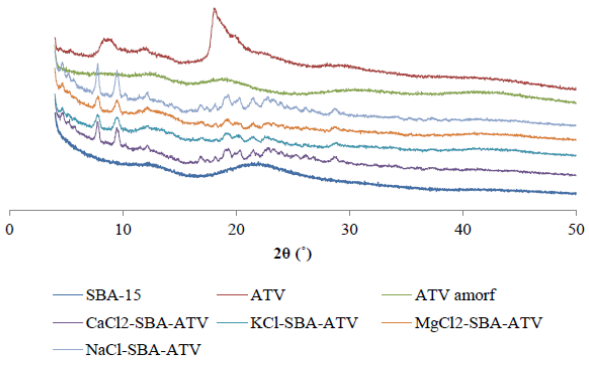

Figure 3 Diffractogram overlay of intact, amorphous and SBA-loaded atorvastatin Ca

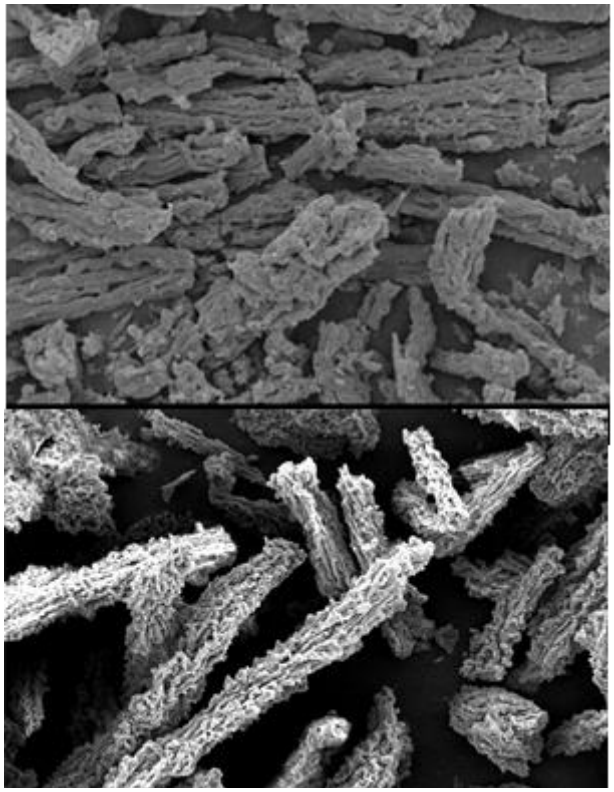

Figure 4 Morphology comparison of unloaded (above) and loaded (below) KCl- SBA-15

cations and anions in the surfactant could be utilized to modify the pore properties of SBA-15 [19].

According to Sing [22], the nitrogen adsorption can also be used to determine the physisorption mechanism of a porous material was a monolayer or multilayer adsorption, capillary condensation or micropore filling. The type IV isotherm curves were generally associated to a mesopores physisorption pattern. The hysteresis was generated in the filling and emptying process by capillary condensation [22]. Along with the pore properties data on Table 1, the isotherm curves in Figure 2 also confirmed that the SBA-15 produced in this study were mesoporous materials with pore size between 2-50 nm.

Atorvastatin Ca loaded SBA-15 was generated by immersing SBA-15 into solution of Atorvastatin Ca (5 mg/ml) in methanol. The solvent was removed by heating at 80ºC under stirring. The amorphous (ATV amorf) were prepared by the same method without SBA-15 added. These samples were subjected to further analysis.

The diffractograms overlay in Figure 3 showed the crystallinity transformation from the intact atorvastatin Ca to the amorphous and loaded into SBA-15. The intact ATV had medium peaks at 5.13º and 8.10º and a large peak at 17.99º 2θ The intact ATV was actually similar to the diffractogram of atorvastatin Ca polymorph form V from Teva Pharmaceutical Industries Ltd with two medium peaks at 5.3+0.2º and 8.3-0.2º 2θ and one large peak in the range 18-23º 2θ [23]. Meanwhile the SBA-15 and amorphous ATV were confirmed as amorph particles without any peak in the diffractograms. The crystal transformation is the result of the recrystallization method in SBA loading process and inhibition of crystal growth in the pore. The morphology comparison of unloaded and loaded SBA-15 presented in Figure 4. The fiberlike SBA-15 transform into fiber covered with spikes from drugs recrystallization. The medium peaks in loaded SBA-15 diffractogram likely the results from those crystal in the surface of SBA-15.

For FT-IR analysis, the sample were prepared in a pressed KBr pellet and run for single scan over the range 4000-400 cm^{-1}. Figure 5 presented the comparison of IR spectra of intact ATV, SBA-15 and ATV loaded SBA of each type of SBA-15 synthesized in this study. ATV

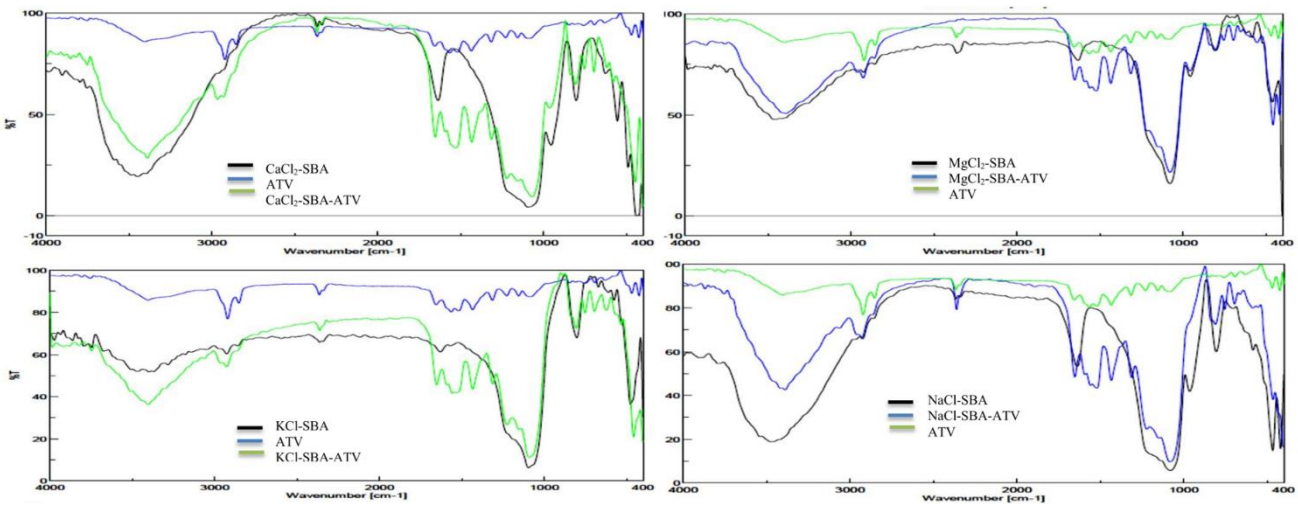

Figure 5 FT-IR spectra of atorvastatin Ca, unloaded and loaded SBA-15

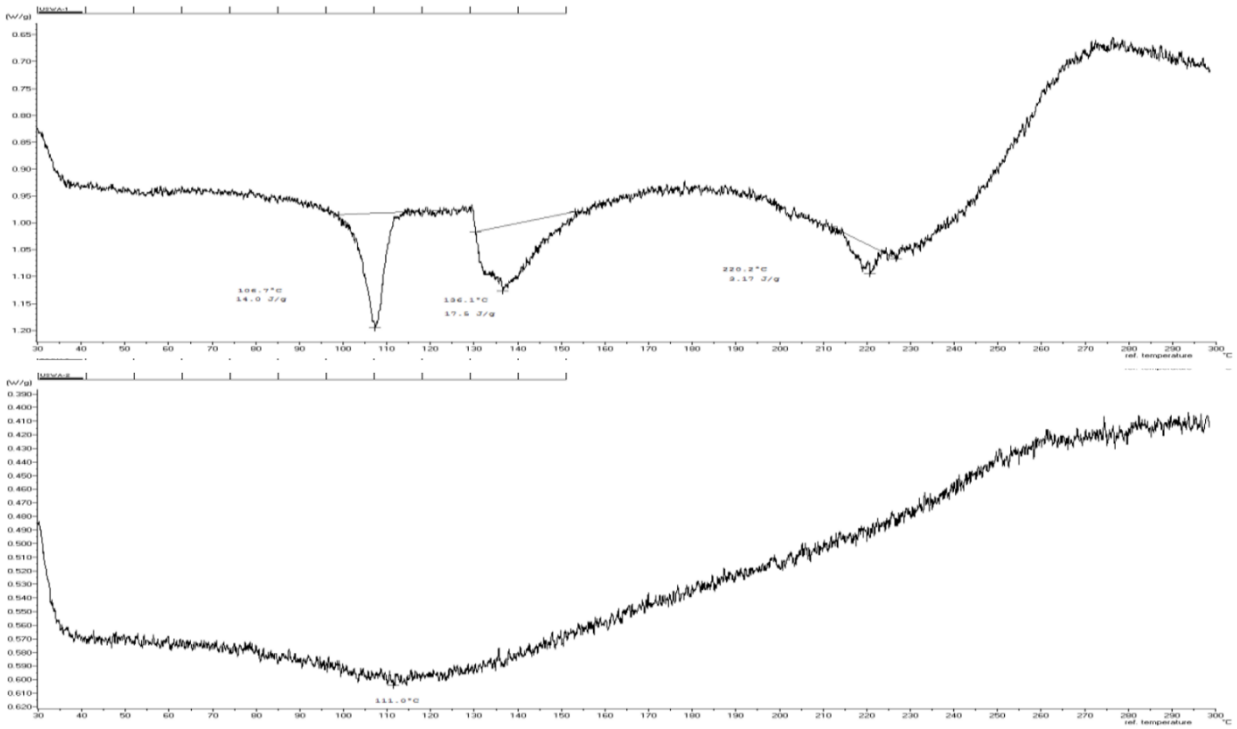

Figure 4 Thermogram comparison of atorvastatin Ca (above) and loaded KCl-SBA-15 (below)

characteristic for infrared absorption bands were found at 3365.5 for -OH, 3228.3 for -NH, 1651.7 for -C=O, 2903.5 for -CH and 1595.1 for -C=C [24]. Each ATV-SBA showed those peaks with a decreased intensity in some samples.

Thermography analysis was conducted to characterized the thermal properties of SBA-15, drug model (ATV) and ATV loaded SBA-15. In this study, the Differential Thermal Analysis were conducted with Linseis STA PT 1600 in the temperature range of 30-300ºC. Thermogram in Figure 6 presented that ATV exhibit three peaks at 106.7ºC that likely from the water molecule removal, wide curve with peak at 136.1ºC that cover both theoretical Tg and Tm of intact atorvastatin (144-155.8ºC), and ATV decomposition peak at 220.2ºC [24]. After the atorvastatin Ca loaded into silica mesoporous materials, there is no peak observed that indicate mostly atorvastatin Ca has lost the crystallinity and transform to the amorphous state.

After a complete characterization, all SBA-ATV were tested for the atorvastatin Ca dissolution profile. According to FDA, the dissolution test of atorvastatin Ca was carried out in 900 ml 0.05 M phosphate buffer pH 6.8 using dissolution apparatus type II, 75 rpm, 37ºC ± 0.5ºC. For comparison, the intact and amorphous atorvastatin Ca were tested in the same condition. The dissolution profile for 30 minutes can be seen in Figure 7. In 30 minutes, only 50.78% of intact atorvastatin Ca was dissolved in the media, meanwhile the highest ATV dissolved were exhibit by NaCl-SBA-ATV for 92.47%. The amorphous drug also has Qt (30) relatively higher than intact atorvastatin Ca. This is the result of crystal form transformation after loaded into the SBA-15. The amorphous form of particles was relatively unstable compared to the crystal form of the same drug, so in a condition where it exposed to a solvent, the amorphous particle would dissolved faster since it only requires low energy to break the intermolecular bond between molecules in the particle. The dissolved amount of atorvastatin Ca loaded in NaCl-SBA were higher compared to KCl-SBA. According to data of pore properties (table 1) of each type of SBA-15, both NaCl and $MgCl_2$ have a higher BET surface area compared to the other mono or multivalent chloride salts. This findings according to Noyes-Whitney equation, that dissolution rate of a drug affected by the contact surface area of drug and dissolution media.

The $CaCl_2$-SBA-ATV exhibit a lower dissolution rate compared to the amorphous atorvastatin Ca. According to Shen, the pore size have a role in dissolution rate of drug loaded in SBA-15 since the media need to get into the pore to dissolved the drug inside. The $CaCl_2$-SBA have a small pore and it likely the root of slow dissolution rate despite it has high BET surface area. ChemSketch was used to design the spatial dimension of atorvastatin Ca molecules, the particle was approximately 2 x 1.5 nm in size meanwhile the average pore size is only slightly higher, 3.6346 nm. This indicate that the abnormality from the dissolution profile was the result of the small pore size of the $CaCl_2$-SBA.

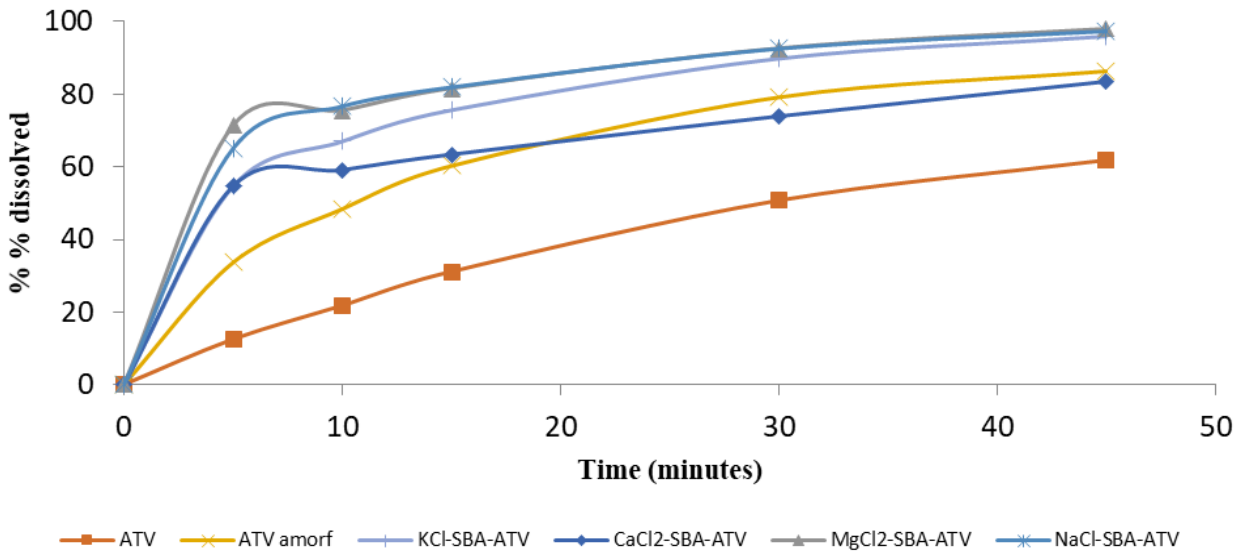

Figure 5 Dissolution profile of intact atorvastatin Ca, amorphous atorvastatin Ca, and atorvastatin Ca loaded SBA-15 in 0.05 M phosphate buffer pH 6.8

4. CONCLUSION

Chloride salts addition facilitated a simple micelle formation of Pluronic P123 as templates for SBA-15 synthesis in room temperature. Various chloride salts addition exhibit different SBA-15 pore properties. Atorvastatin Ca loaded SBA-15 perform better dissolution profile compared to intact atorvastatin Ca by increasing the surface area and crystal to amorph transformation.

AUTHORS' CONTRIBUTIONS

Each author contributes to the research and manuscript equally.

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REFERENCES

[1]. Wang J, Flanagan DR. Chapter 13 - Fundamentals of Dissolution. In: Qiu Y, Chen Y, Zhang GGZ, Liu L, Porter WR, editors. Developing Solid Oral Dosage Forms. San Diego: Academic Press; 2009. p. 309–18. https://doi.org/https://doi.org/10.1016/B978-0-444-53242-8.00013-8

[2]. Dayal S. Dissolution Rates of Poorly Soluble Solids in Mixed Organic Solvents [Internet]. University of Wisconsin--Madison; 1970. Available from: https://books.google.co.id/books?id=YtFsAAAAMAAJ

[3]. Abdou HM. Dissolution, Bioavailability & Bioequivalence [Internet]. Mack; 1989. Available from: https://books.google.co.id/books?id=a_1sAAAAMAAJ

[4]. Dokoumetzidis A, Macheras P. A century of dissolution research: From Noyes and Whitney to the Biopharmaceutics Classification System. Int J Pharm. 2006;321(1):1–11. https://doi.org/https://doi.org/10.1016/j.ijpharm.2006.07.011

[5]. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. Int Sch Res Not. 2012;2012.

[6]. Vemula VR, Lagishetty V, Lingala S. Solubility enhancement techniques. Int J Pharm Sci Rev Res. 2010;5(1):41–51.

[7]. Kumar A, Sahoo SK, Padhee K, Kochar PS, Sathapathy A, Pathak N. Review on solubility enhancement techniques for hydrophobic drugs. Pharm Glob. 2011;3(3):1–7.

[8]. Kadam S V, Shinkar DM, Saudagar RB. Review on solubility enhancement techniques. IJPBS. 2013;3(3):462–75.

[9]. Zhang Y, Zhi Z, Jiang T, Zhang J, Wang Z, Wang S. Spherical mesoporous silica nanoparticles for loading and release of the poorly water-soluble drug telmisartan. J Control Release. 2010;145(3):257–63.

[10]. Maleki A, Kettiger H, Schoubben A, Rosenholm JM, Ambrogi V, Hamidi M. Mesoporous silica materials: From physico-chemical properties to

enhanced dissolution of poorly water-soluble drugs. J Control Release. 2017;262:329–47.

[11]. Mellaerts R, Mols R, Jammaer JAG, Aerts CA, Annaert P, Van Humbeeck J, et al. Increasing the oral bioavailability of the poorly water soluble drug itraconazole with ordered mesoporous silica. Eur J Pharm Biopharm. 2008;69(1):223–30.

[12]. Van Speybroeck M, Barillaro V, Do Thi T, Mellaerts R, Martens J, Van Humbeeck J, et al. Ordered mesoporous silica material SBA-15: a broad-spectrum formulation platform for poorly soluble drugs. J Pharm Sci. 2009;98(8):2648–58.

[13]. He Y, Liang S, Long M, Xu H. Mesoporous silica nanoparticles as potential carriers for enhanced drug solubility of paclitaxel. Mater Sci Eng C. 2017;78:12–7.

[14]. Bukara K, Schueller L, Rosier J, Martens MA, Daems T, Verheyden L, et al. Ordered mesoporous silica to enhance the bioavailability of poorly water-soluble drugs: Proof of concept in man. Eur J Pharm Biopharm. 2016;108:220–5.

[15]. Knapik-Kowalczuk J, Kramarczyk D, Chmiel K, Romanova J, Kawakami K, Paluch M. Importance of Mesoporous Silica Particle Size in the Stabilization of Amorphous Pharmaceuticals—The Case of Simvastatin. Pharmaceutics. 2020;12(4):384.

[16]. Zhao D, Yang P, Melosh N, Feng J, Chmelka BF, Stucky GD. Continuous mesoporous silica films with highly ordered large pore structures. Adv Mater. 1998;10(16):1380–5.

[17]. Yu C, Tian B, Fan J, Stucky GD, Zhao D. Salt effect in the synthesis of mesoporous silica templated by non-ionic block copolymers. Chem Commun. 2001;(24):2726–7.

[18]. Yu J, Shi J-L, Chen H-R, Yan J-N, Yan D-S. Effect of inorganic salt addition during synthesis on pore structure and hydrothermal stability of mesoporous silica. Microporous mesoporous Mater. 2001;46(2–3):153–62.

[19]. Kubo S, Kosuge K. Salt-induced formation of uniform fiberlike SBA-15 mesoporous silica particles and application to toluene adsorption. Langmuir. 2007;23(23):11761–8.

[20]. Johansson EM. Controlling the Pore Size and Morphology of Mesoporous Silica [Internet]. Linköping Studies in Science and Technology. Thesis NV - 1451. [Nanostructured Materials, Department of Physics, Chemistry and Biology, Linköping University]: Linköping University Electronic Press; 2010. Available from: http://liu.diva-portal.org/smash/get/diva2:439011/FULLTEXT01.pdf

[21]. Denkova AG, Mendes E, Coppens M-O. Effects of Salts and Ethanol on the Population and Morphology of Triblock Copolymer Micelles in Solution. J Phys Chem B. 2008;112(3):793–801. https://doi.org/10.1021/jp075114c

[22]. Sing KSW. Physisorption of nitrogen by porous materials. J Porous Mater. 1995;2(1):5–8.

[23]. Ayalon A, Levinger M, Roytblat S, Niddam V, Lifshitz R, Aronhime J. Polymorphic Form of Atorvastatin Calcium [Internet]. United States: United States Patent; USOO741 1075B1, 2000. p. 8. Available from: https://patents.google.com/patent/US7411075B1/en

[24]. Sonje VM, Kumar L, Meena CL, Kohli G, Puri V, Jain R, et al. Atorvastatin calcium. In: Profiles of Drug Substances, Excipients and Related Methodology. Elsevier; 2010. p. 1–70.