

The Effect of Cyclodextrin Addition Towards Preparation of Atorvastatin Nanoparticle for Hypercholesterolemia Drug

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Abstract: Atorvastatin is a material used in the pharmaceutical world as hypercholesterolemia drug. The addition of cyclodextrin as encapsulation media atorvastatin are expected to provide the amorphous nature of the material. This research will study the effect of adding cyclodextrin to dry milling process atorvastatin then characterized using Particle Size Analyzer (PSA), X-Ray Diffraction (XRD) and Scanning Electron Microscope (SEM). PSA test results showed that atorvastatin sample before milling was measured at 2386.7 ± 630.5 nm. After milling with addition of cyclodextrin resulted on size of 127.1 ± 503.2 nm. While the control without the addition of cyclodextrin after milling resulted in size of 446.6 ± 112.4 nm. XRD characterization results indicate that the formation of the amorphous phase is characterized by a widening of the peaks in the XRD data. SEM image further showed the amorphous characteristic of resulted atorvastatin nano particle.. In conclusion, the addition of cyclodextrin was capable of producing amorphous properties towards nano-atorvastatin.

Key words: Atorvastatin • Cyclodextrin • Dry milling • Particle size • Amorphous

INTRODUCTION

Atorvastatin is a chemical compound with molecular formula $C_{33}H_{35}FN_2O_5$ with IUPAC name of acid (3*R*,5*R*)-7-[2-(4-fluorofenil)-3-fenil-4-(fenilcarbamoil)-5-propan-2-ilpirol-1-il]-3,5-dihidroksiheptanoat. Atorvastatin is commonly used in the pharmaceutical world as hypercholesterolemia drug. Atorvastatin works by reducing level of TL, LCL-C, apo B and TGs effectively by inhibiting 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase (enzymes involved in the biosynthesis of cholesterol) in the liver so that it will encourage the reduction of circulating LDL cholesterol. In addition, atorvastatin is also proved to protect the blood vessels (vasculo protective) so as to prevent cardiovascular disease.

Since the atorvastatin patent expiration in November 2011, many pharmaceutical companies compete to develop products based on atorvastatin for anti-hypercholesterolemia application. One of biggest

challenges of development of this drug is its low solubility, especially at low pH (which is the condition of the hull), making it difficult to be administered.

Several researchers have developed methods for particle size reduction [1,2] and the transformation of amorphous to crystalline [3]. One new approach considered highly prospective to overcome the problems is by using nanotechnology. Particle size reduction to nano scale will improve dissolution rate as the effects of increased surface area of the particles [4]. In addition, the formation of the amorphous structure which usually occurs on nanoparticle will contribute to better solubility.

Encapsulation of Atorvastatin nanoparticle in polymer systems will be providing protection against active substances as well as forming the dual function thus improving solubility. Oligosaccharide cyclodextrin is often used as a medium for the encapsulation of active substances for medicines that will improve the water solubility, stability and bioavailability of the drug in the body by forming active substance-cyclodextrin complex

[4]. In this study, the effect of addition of cyclodextrin as medium for encapsulation of Atorvastatin nanoparticle will be investigated.

MATERIALS AND METHODS

Atorvastatin is obtained from the Laboratory of Agro Industrial Technology and Biomedical. In this study, cyclodextrin was mixed with atorvastatin using High Energy Ball Mill (HEM E3D) for 4 hours. As the control, atorvastatin was milled without the addition of cyclodextrin. Samples were then characterized using Particle Size Analyzer (PSA) Delsa Nano, Beckman Coulter Inc. X-ray Diffraction (Rigaku Miniflex 600) to measure the properties of crystallinity of atorvastatin, Difference Scanning Calorimeter (DSC) for measuring the temperature of the material changes and characterization of Scanning Electron Microscope (SEM) to see changes in particle shape.

RESULTS AND DISCUSSION

Figure 1 shows the results of measurements of the particles in the atorvastatin with and without the addition of cyclodextrin. Atorvastatin before milling (Figure 1a) has a size of 2386.7 ± 630.5 nm. Process without the addition cyclodextrin (Figure 1b) produced particle with size 446.6 ± 112.4 nm, whereas without the addition of cyclodextrin (Figure 1c) produce particle with size of 503.2 ± 127.1 nm. This suggests that the addition of cyclodextrin during milling resulted on particle agglomeration.

Figure 2 shows the SEM image of atorvastatin with and without the addition of cyclodextrin in the milling process at 10000x magnification. Figure 2(c) shows that addition of cyclodextrin during milling resulted on amorphous form of atorvastatin. This could be due to the bond between atorvastatin with cyclodextrin producing by-products, such as water vapor.

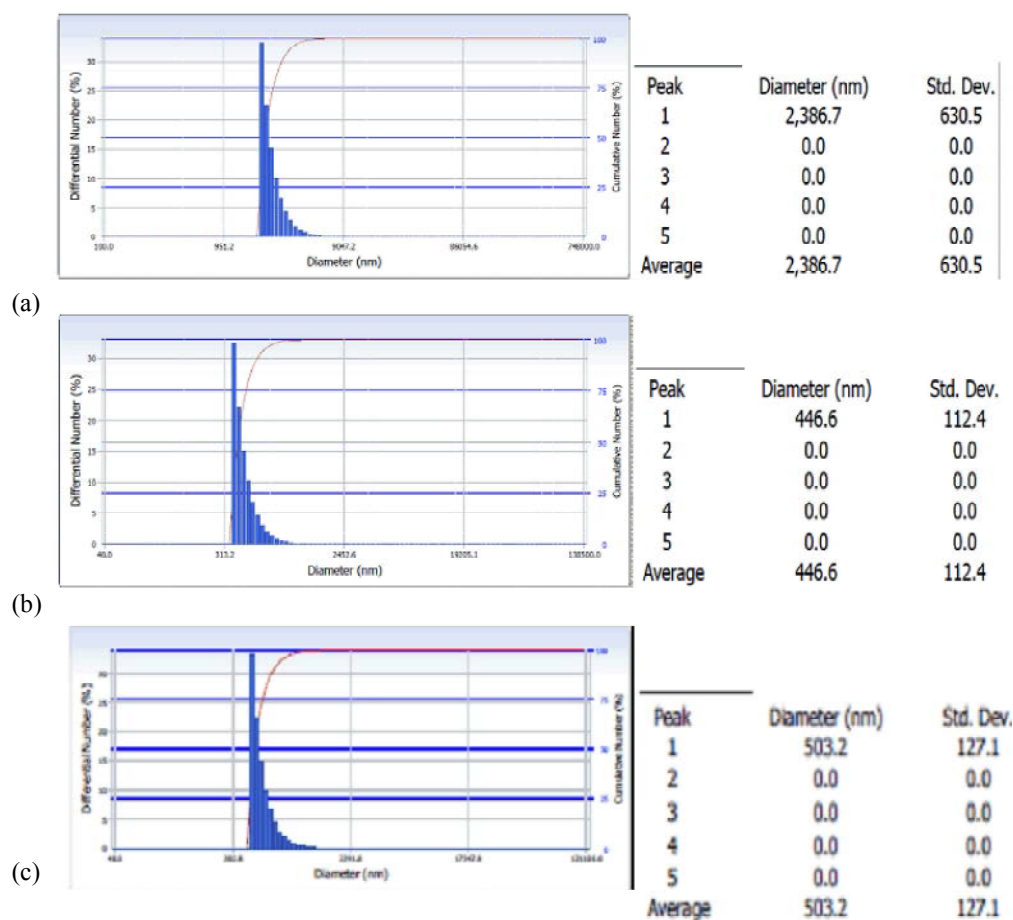


Fig. 1: Particle size of Atorvastatin, (a) before milling, (b) after dry milling, and (c) after wet milling

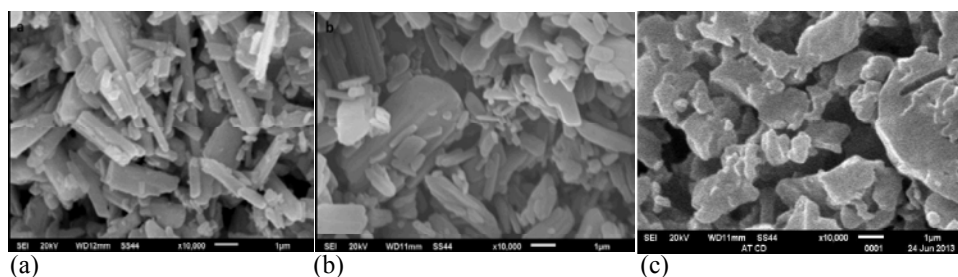


Fig. 2: The SEM image of Atorvastatin, (a) before milling, (b) after milling (without cyclodextrin), dan (c) after milling (with cyclodextrin)

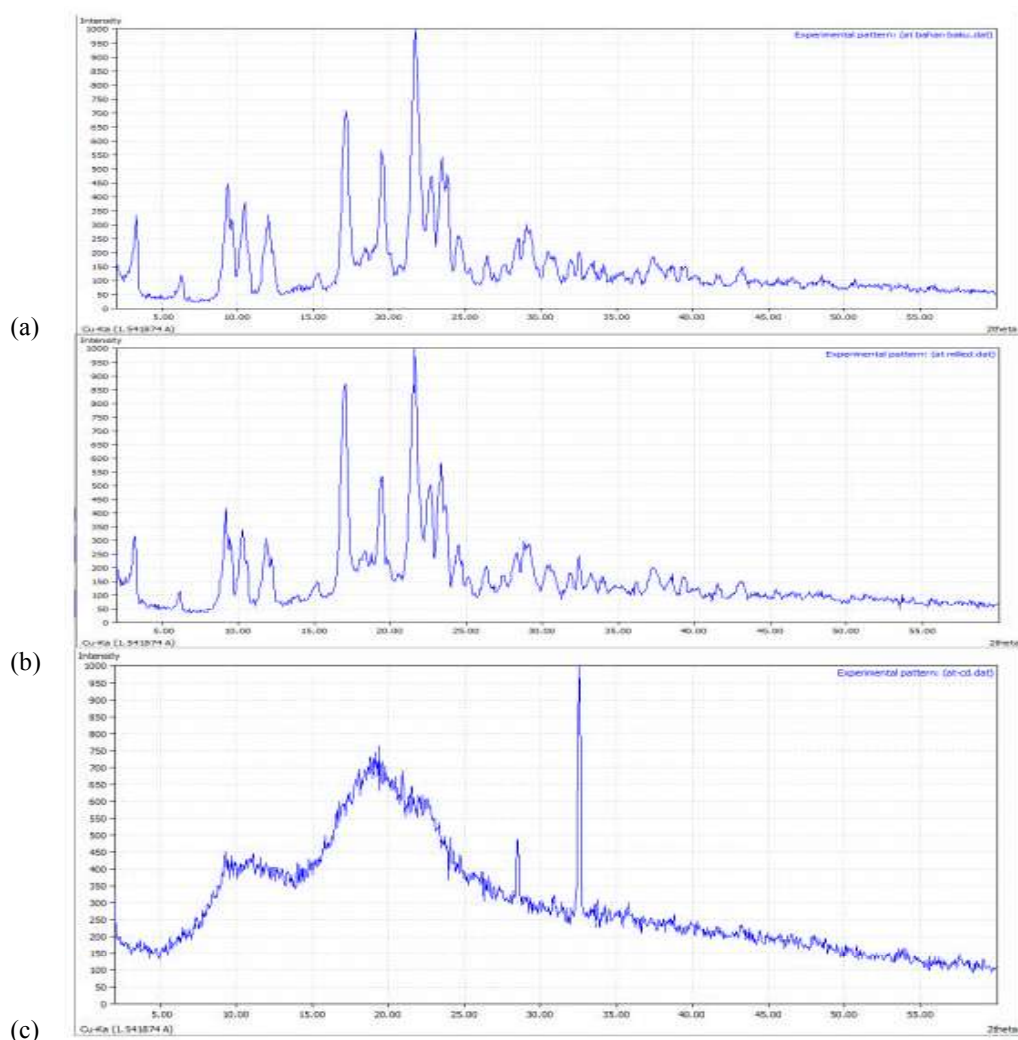


Fig. 3: X-ray diffraction pattern of Atorvastatin, (a) before milling, (b) after milling (without cyclodextrin), and (c) after milling (with cyclodextrin)

Figure 3 shows the results of X-ray diffraction particle of encapsulated atorvastatin before and after milling. The formation of amorphous phase in the XRD pattern of atorvastatin after addition of cyclodextrin can be observed obviously.

CONCLUSION

The addition of cyclodextrin in the milling process produced amorphous phase of encapsulated nano-atorvastatin on nano-atorvastatin.

Addition of cyclodextrin did not change the size of the particle significantly, as it is still in nanometer size.

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