

Atorvastatin ascorbic acid cocrystal strategy to improve the safety and efficacy of atorvastatin

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Abstract

The study was aimed to investigate the effect of dissolution enhancement on the hypolipidemic effect and hepatotoxicity of the drug in hyperlipidemic rats. Atorvastatin ascorbic acid cocrystals were prepared by phase solution methods and characterized by Fourier transformation infrared spectroscopy, differential scanning calorimetry, scanning electron microscopy, X-Ray powder diffraction. Results of characterization confirmed that atorvastatin ascorbic acid cocrystals exhibited particle size was 221 nm. In *in vitro* study, results of dissolution test showed that the release of atorvastatin was increased to 1.6 folds. From *In vivo* study results, it was observed that in atorvastatin ascorbic acid cocrystals treated rats, serum total cholesterol, triglycerides, liver transaminase levels were significantly decreased, and liver glutathione activity was increased. In conclusion, atorvastatin ascorbic acid cocrystals therapy exhibited less hepatotoxicity in presence of ascorbic acid when compared to atorvastatin alone therapy and also the efficacy of therapy was improved.

Keywords

cocrystal technology, atorvastatin, ascorbic acid, atorvastatin ascorbic acid cocrystals

Introduction

Atorvastatin is a synthetic lipid modifier that has been approved for atherosclerosis and cardiovascular disease as an effective therapy. It acts by inhibiting β -hydroxy β -methylglutaryl CoA reductase, which results in lower serum total and LDL cholesterol, apoB and triglyceride levels while increasing HDL cholesterol levels. The drug has poor water solubility with a recorded solubility value

of 0.011 mg/L with low solubility and a high intestinal clearance and metabolism of the first pass. The drug has a narrow absorption window in accordance with the biopharmaceutical classification system (Davis 2005). In addition to its narrow absorption window, the acidity (pKa 4.33) of the drug led to poor solubility and dissolution in the acidic environment of the upper GIT, thereby increasing the number of doses required to achieve therapeutic benefits, but leading to hepatic abnormalities

and renal failure (Motola et al. 2007; Shete et al. 2010). Therefore, the improvement of the dissolution rate in the acid environment is expected to improve the oral bioavailability of atorvastatin to minimize the toxicity of atorvastatin. The authors used various techniques to fasten the dissolution rate of drugs with drug crystalline structure and/or crystal size being the most commonly used (Khadka et al. 2014). This can be achieved through reduction of the particle size, controlled crystallization and preparation of solid dispersion with various hydrophilic polymers. Crystal modification with inert pharmaceutical additive cocrystallization is an emerging technique for which great expectations are expected (Chow et al. 2014; Li et al. 2014; Hong et al. 2015; Qiu and Li 2015). Cocrystallization is a method for modifying the physical and chemical properties of drugs such as solubility, dissolution rate, stability, hygroscopicity and compression without altering their pharmacological behavior (Schultheiss and Newman 2009). Cocrystals are very promising in the improvement of pharmaceutical properties such as dissolution, bioavailability, compressibility, physical stability and photo stability (Aitipamula et al. 2012; Sun 2013; Azizi et al. 2014; Duggirala et al. 2014; Maeno et al. 2014; Sarkar and Rohani 2014). Ascorbic acid, gallic acid, nicotinamide, citric acid, aglutamic acid, histidine, urea, saccharine, glycine, succinic acid, sucrose and alpha ketoglutaric acid were successfully used to develop drug crystals that speed up the solution rate (Pathak et al. 2013; Shinde et al. 2014). Ascorbic acid is a water soluble vitamin, obtained endogenously as well as dietary sources, natural products such as fresh fruits and leafy vegetables (Haytowitz 1995; Smirnoff 2000). Ascorbic acid can protect lipids and lipoproteins in cell membranes from oxidative damage caused at an early stage by toxic free radicals (Acharya et al. 2008), protective effect on hepatocellular damage (Netke et al. 1997). Accordingly, the main aim of this work was to investigate the feasibility of ascorbic acid as a co-crystal former for rapid dissolution of atorvastatin, and evaluate efficacy, safety atorvastatin on hyperlipidemic rats.

Materials and methods

Materials

Atorvastatin (Aurabindo Pharma, India). Ascorbic acid, Methanol (Loba Chemie, Mumbai, India). Total Cholesterol, Triglycerides, SGOT, SGPT Kits (Coral Clinical system, Tulip Diagnostics, Hyderabad), Wistar albino rats (Mahaveer Enterprises, Hyderabad).

Atorvastatin ascorbic acid cocrystals preparation

Co-crystal formation was achieved using phase solubility studies, equimolar ratio of atorvastatin and ascorbic acid (1:1) were dissolved in methanol and stirred under slight heating until a clear solution was obtained. The solution is immediately filtered using a funnel and whatman filter

paper. The solution is allowed to dry overnight at room temperature. The obtained cocrystals were stored in desiccators until they were characterized.

Drug content determination

Co-crystals were dissolved in methanol (1 mg / ml), volume adjusted to 50 ml distilled water and filtered through a membrane filter of 0.45 μ m. Drug content was quantified using double beam UV-Visible Spectrophotometer (at 246 nm) (Shimadzu-1800, Japan) (GaDaDe et al. 2017).

Fourier transformation infrared (FT-IR) spectroscopy

Powdered samples were compressed to disks after mixing with potassium bromide of spectroscopic grade. The FT-IR (Alpha-E Bruker FT-IR) spectra of these disks were recorded in the range of 4000 to 400 cm^{-1} , under potassium bromide diffuse reflectance mode using a pyroelectric detector. The collected data were analyzed using FT-IR spectroscopy Software.

Differential scanning calorimetry (DSC)

Powdered samples (2 mg) were encapsulated in an aluminum pan that was crimped onto the furnace before mounting. The samples have been heated from 30 °C to 200 °C at a rate of 10 °C per minute. The thermal events were monitored with dry nitrogen flowing at a rate of 20 ml/min (DSC (TA SDT 2960 DSC (USA)). The whole process was under computer control employing Pyris software for recording and analyzing the data.

Scanning electron microscopy (SEM)

Powder samples were mounted on double sided adhesive tape and sputter coated with gold palladium thin layer. Scanning electron photographs (SEM, JSM 6360 LV, Joel Ltd., Tokyo, Japan) were taken with an electron beam of an accelerating voltage of 10 kV using secondary electron image (SEI) as the detector at 50 KX magnifications.

X-Ray powder diffraction (XRD)

Sample was analyzed between the interval 5–50° 2 θ with scanning speed of 2°/min using X-ray diffraction system (Philips Analytic X-Ray – PW 1729; Philips, Almelo, The Netherlands). The diffraction pattern was measured with generator tension (voltage) and generator current of 40 kV and 30 mA respectively.

In vitro dissolution studies

Drug releases from cocrystals were determined using USP type II (paddle) dissolution method. Atorvastatin and its cocrystal formulations equivalent weight 100 mg were placed in 900 ml/ 0.05 M phosphate buffer pH 6.8, 37 \pm 0.5 °C and stirred at 75 rpm. At definite time intervals, aliquot

of the samples were withdrawn, filtered through Millipore filter (0.45 μm) and analyzed UV spectrophotometrically at 246 nm. In order to maintain sink condition, equal quantity of fresh dissolution medium maintained at the same temperature was added after each sampling.

Evaluation of safety and efficacy of atorvastatin ascorbic acid cocrystal formulation

Animals

Wistar albino rats of either sex weighing 190 ± 20 g were obtained from animal house attached to the institute. Animals were exposed to natural day and night cycles with ideal laboratory condition in terms of ambient temperature (22 ± 2 °C) and humidity (50–60%). They were fed with rat pellet feed and tap water given *ad libitum*. All animals were maintained according to CPCSEA guidance (439/PO/RE/S/01/CPCSEA). The experiments were carried out after obtaining the permission of Institutional Animal Ethics Committee (Approval number; IAEC/04/2016/17/PG).

Preparation of hyperlipidemic rats (Sampathkumar et al. 2011)

Hyperlipidemic rats were prepared by feeding of high fat diet composed normal pellet diet 40 gm%, Animal fat 25 gm%, Coconut oil 6 gm% Fructose 10 gm%, casein 6 gm%, Egg protein 12 gm%, Minerals and vitamins 0.5 gm%, NaCl 0.5 gm%) for 8 weeks.

Group I: Normal rats

Hyperlipidemic rats were dividing into following groups

Group II: High fat diet feeding rats

Group III: Unprocessed atorvastatin 7.5 mg/kg orally

Group IV: Unprocessed atorvastatin 75 mg/kg orally.

Group V: Atorvastatin ascorbic acid cocrystals 7.5 mg/kg orally.

Group VI: Atorvastatin ascorbic acid cocrystals 75 mg/kg orally.

Atorvastatin and atorvastatin ascorbic acid co-crystals were administered into rats in the form of an aqueous suspension in 0.5% sodium carboxymethylcellulose (Na-CMC). Blood was collected from retro orbital plexus at 0 day, 1st, 2nd, 4th and 8th week, serum was separated, subjected for estimation of serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), triglycerides, total cholesterol. At the end of 8th weeks of treatment rats were euthanized using CO₂ chamber, isolate the liver, and then homogenate, supernatant was used for estimation of reduced glutathione.

Statistical analysis

The data generated during the study were subjected to Dunnet's test, data to assess the statistical significance. 'p'; value less than 0.05 were considered as statistically

significant. Significant at **p < 0.01; *p < 0.05, a: Comparison between ATV 7.5 mg/kg orally vs AAC 7.5 mg/kg orally; b: Comparison between ATV 75 mg/kg orally vs AAC 75 mg/kg orally.

Results and discussion

Percentage of yield

Atorvastatin ascorbic acid cocrystals are developed with yield of 97%, drug content range was 96 ± 1.5 w/w to 99 ± 1.21 w/w.

FT-IR spectroscopy

Unprocessed atorvastatin shows an O – H stretching vibration of 3748.44 cm^{-1} , which is reduced to 3732.69 cm^{-1} , indicating hydrogen bonding of ascorbic acid carbonyl oxygen to the atorvastatin O-H group. Amide group of atorvastatin exhibits carbonyl stretch at 1673.04 cm^{-1} which is reduced to 1650.41 confirms the hydrogen bonding between atorvastatin and ascorbic acid (Fig. 1).

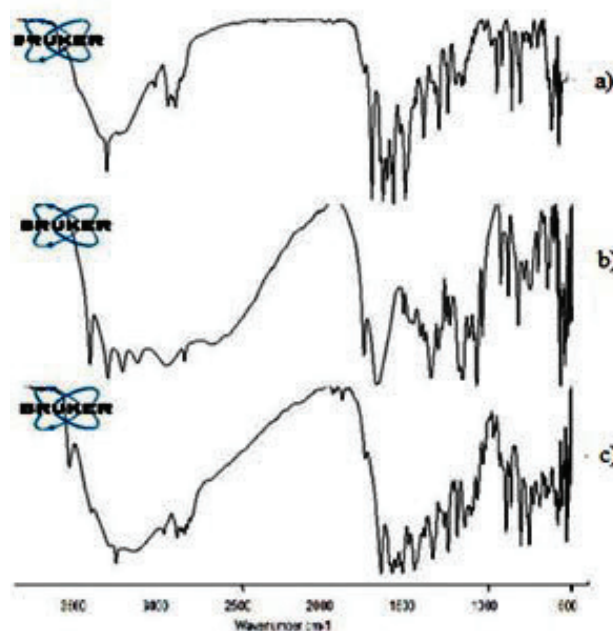


Figure 1. IR spectra of **a** Atorvastatin; **b** ascorbic acid; **c** atorvastatin ascorbic acid cocrystal.

Differential scanning calorimetry

Ascorbic acid co-crystal atorvastatin was shown to have a higher melting point of 267.43 °C when compared to individual atorvastatin (163.46 °C) and Ascorbic acid (195.92 °C). This confirms the co-crystal formation and physical interaction of atorvastatin with Ascorbic acid through hydrogen bonding, which increased the energy value in crystals compared to atorvastatin (Fig. 2).

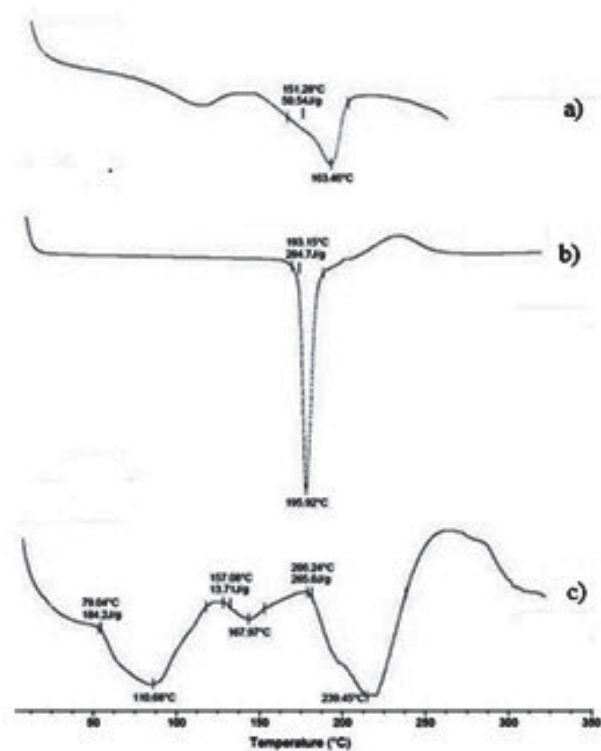


Figure 2. DSC thermogram of **a** atorvastatin; **b** ascorbic acid; **c** atorvastatin ascorbic acid cocrystal.

Scanning electron micrograph

Atorvastatin appeared in large and irregular formed particles, while ascorbic acid was granular. Atorvastatin and ascorbic acid cocrystals showed fine particles with uniform dimensions and SEM results showed a reduction in particle size to 221 nm (Fig. 3).

Powder X-ray diffraction

Cocrystal is a supramolecular synthon which is formed by the stoichiometric mixing of atorvastatin with ascorbic acid. The interaction of one molecule with other leads to formation of new crystal lattice which is confirmed by comparing standard XRD values of Atorvastatin, ascorbic acid 21.44, 35.38, respectively, cocrystal exhibited 18.48 this is due to hydrogen bonding the lattice energy has decreased to significant level. This confirms the formation of atorvastatin: ascorbic acid co-crystal formation (Fig. 4). The recorded amendments in the X-ray diffraction, FTIR spectrum and the thermal behavior support the development of a cocrystalline product with the molar ratio of 1:1 being the optimum ratio for co-crystallization. Similar strategy was followed in identification of co-crystallization of neiglitinide and furosemide co-crystal (Bruni et al. 2011; Wang et al. 2013; Sanphui and Rajput 2014).

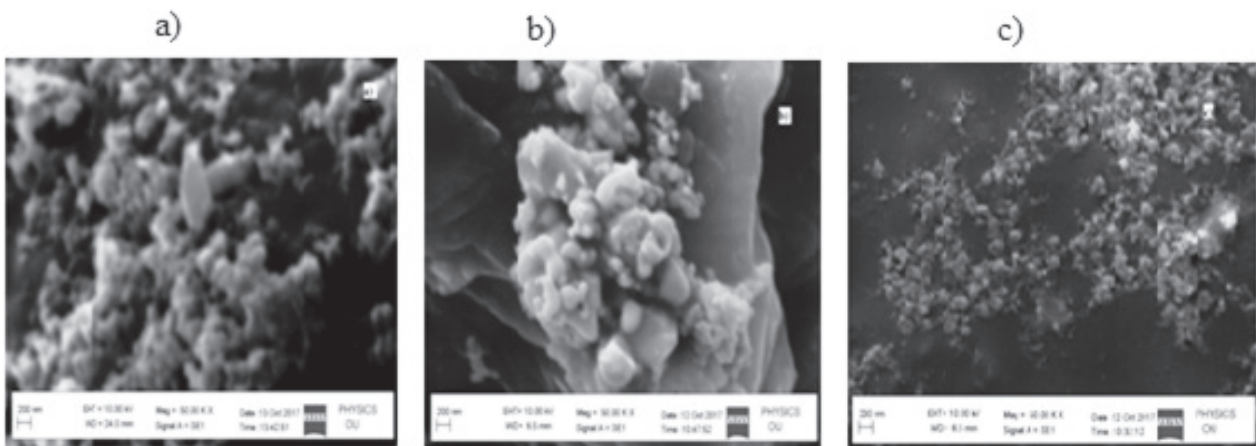


Figure 3. SEM analyses of **a** atorvastatin; **b** ascorbic acid; **c** atorvastatin ascorbic acid cocrystal.

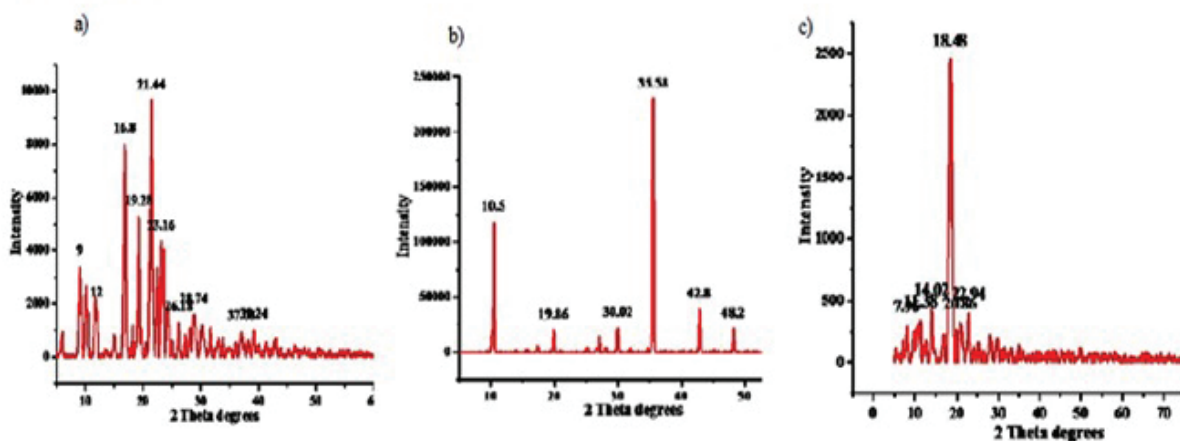


Figure 4. XRD analyses of **a** atorvastatin; **b** ascorbic acid; **c** atorvastatin ascorbic acid cocrystal.

Dissolution studies

The release of atorvastatin was 1.60 fold enhanced by cocrystals in comparison with unprocessed atorvastatin (Fig. 5). The improvement in dissolution was observed after the co-crystallization of different slowly dissolving furosemide (Goud et al. 2012; El Maghraby et al. 2015).

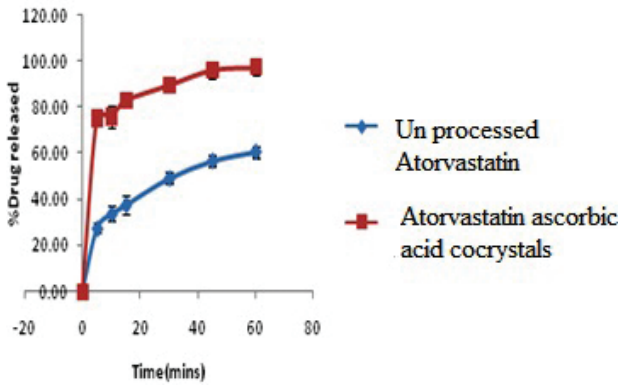


Figure 5. Dissolution profile of atorvastatin and atorvastatin ascorbic acid cocrystal.

Effect of unprocessed ATV and AAC on liver SGPT, SGOT in hyperlipidemic rats

Unprocessed ATV (75 mg/kg, p.o) treated high fat diet rats serum SGPT, SGOT levels were significantly ($*P < 0.05$) increased 52.8%, 51.09%, respectively compared to untreated rats. AAC (75 mg/kg, p.o) treated high fat diet rats serum SGPT, SGOT levels were decreased significantly by 20.9% and 6.79% respectively, compared ATV treated high fat diet rats (Figs 6, 7). Most of statins are metabolized by the liver and damage to this organ was assessed by elevated levels of its aminotransferases SGOT and SGPT. The increase in aminotransferases levels more than three times the upper normal limit indicates a potential liver toxicity (Veillard and Mach 2002; Waters 2005). The hepatoprotective effects of ascorbic acid against liver toxicity caused by carbon tetrachloride, chlorophyrifos, ethanol with significant decreases in SGOT and SGPT levels are investigated in many studies (Clarke and Mills 2005). In accordance with these studies, the SGOT and SGPT levels of co-crystals treated rats have been significantly reduced, which could be the presence of ascorbic acid.

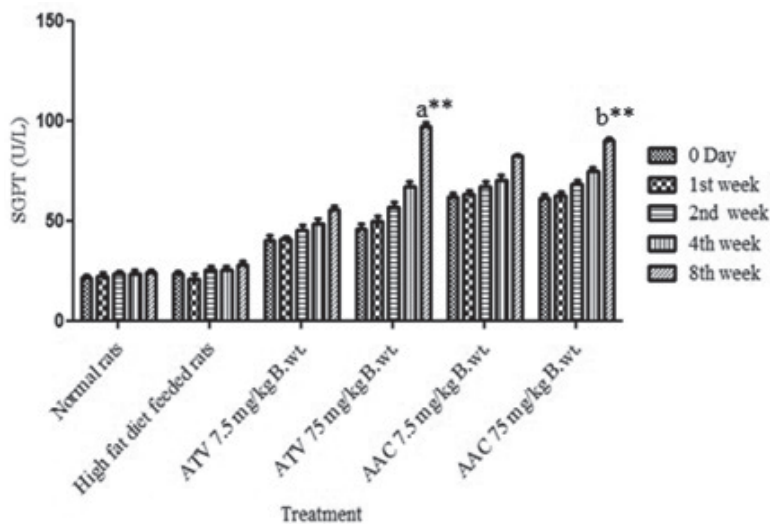


Figure 6. Effect of ATV and AAC on liver SGPT in hyperlipidemic rats.

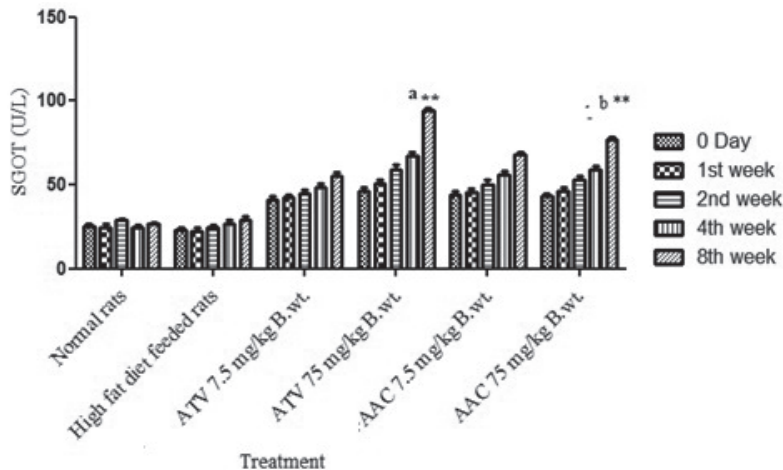


Figure 7. Effect of ATV and AAC on liver SGOT in hyperlipidemic rats.

Effect of unprocessed ATV and AAC on total cholesterol and triglycerides in hyperlipidemic rats

Unprocessed ATV (75 mg / kg orally) treated high fat diet rats with total serum cholesterol and triglycerides (**p < 0.01) decreased 16.3%, 27.8% compared to untreated rats (Figs 8, 9). A significant decrease in total cholesterol and triglycerides was observed in rats given AAC compared to ATVs. This finding is in line with previous reports that demonstrate ascorbic acid hypocholesterol (Le Prell et al. 2014).

Effect of unprocessed ATV and AAC on liver reduced glutathione (GSH) level in hyperlipidemic rats

Unprocessed ATV (75 mg/kg. orally.) treated rat hepatic reduced GSH levels are significantly (p < 0.001***) decreased compared to hyperlipidemic as well as normal rats. However, administration of AAC had the opposite effect, where it significant (p < 0.05*) increased hepatic reduced GSH activities nearly to that of control (Fig. 10). In our bodies, antioxidant molecules are used to scavenge ROS and

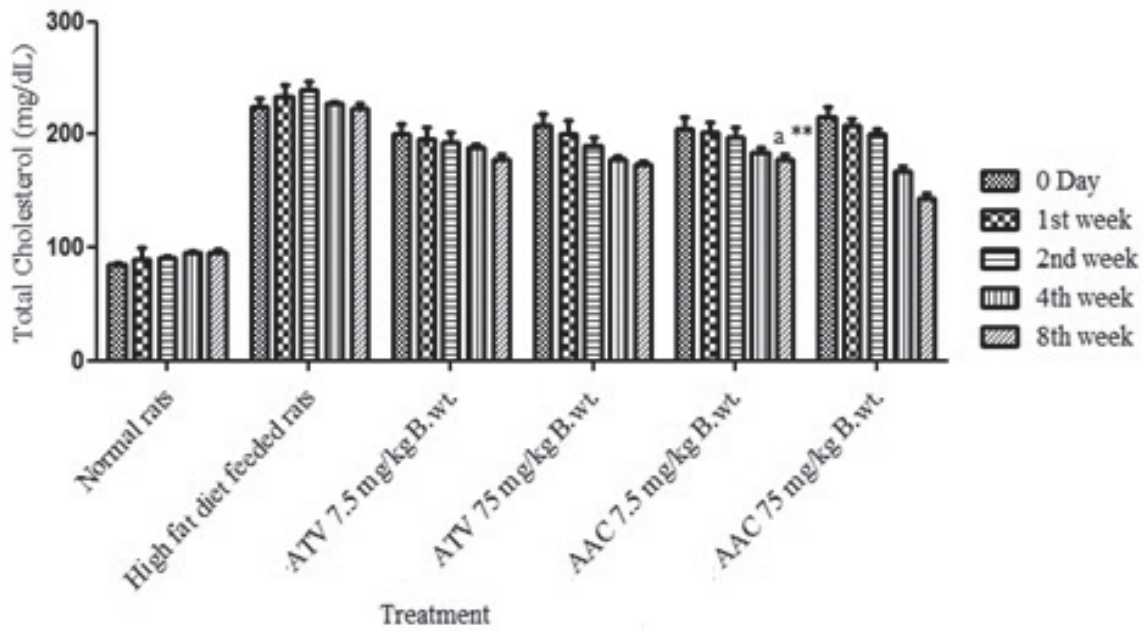


Figure 8. Effect of ATV and AAC on total cholesterol in hyperlipidemic rats.

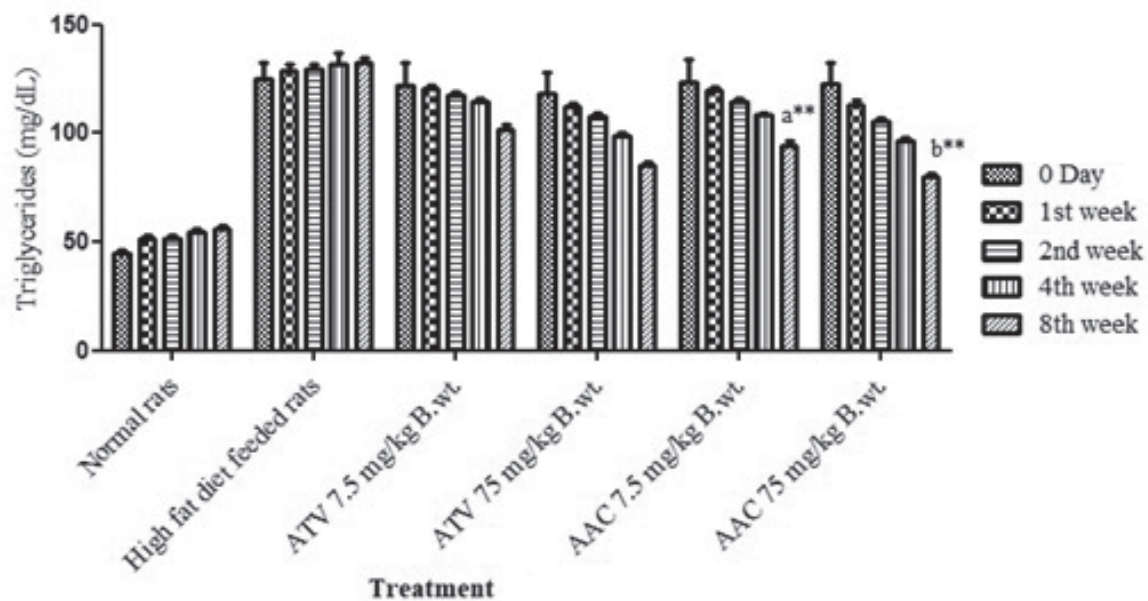


Figure 9. Effect of ATV and AAC on triglycerides in hyperlipidemic rats.

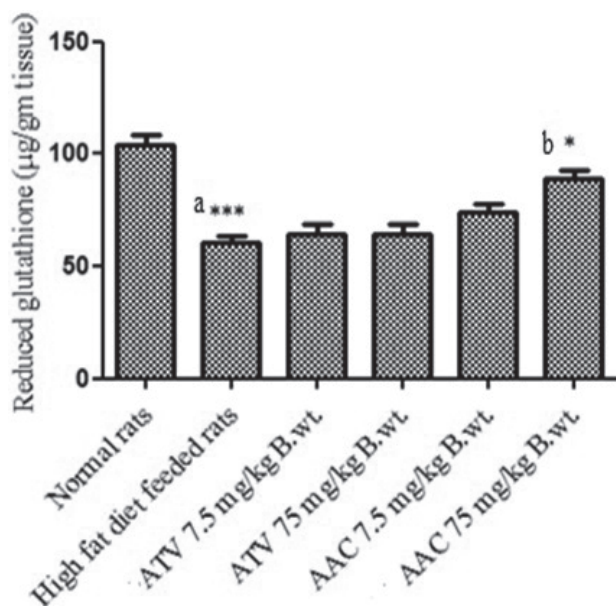


Figure 10. Effect of ATV and AAC on liver reduced glutathione (GSH) in hyperlipidemic rats.

prevent oxidative stress. Intracellular antioxidant reduces GSH scavenges free radicals, and other oxidant species detoxify different xenobiotics and thus convert to its oxidizing form GSSH (Dolphin et al. 1989). As a result, GSH levels decreased due to increased GSSG levels, the GSH / GSSH ratio decreased. ATV damage to the liver as shown by the dose- dependent reduced GSH activity (Heeba and Abd Elghany 2010). In this study, the results suggested that GSH activity was reduced by treatment with ATV and

that it was at least partially normalized with AAC. The antioxidant activity of ascorbic acid thus seems to play a key role in alleviating the hepatic damage caused by ATV.

Conclusion

Phase solubility study of atorvastatin with ascorbic acid at different molar ratios was able to produce co-crystalline solids with enhanced dissolution rate compared with the parent drug. Atorvastatin should be mixed with ascorbic acid at a molar ratio of 1:1 for optimum cocrystallization. Co-crystallization induced dissolution enhancement was able to improve the efficacy of the drug as expressed by reduction in lipid profile and improve the safety of atorvastatin on hyperlipidemic rats compared to the unprocessed atorvastatin.

Conflict of interest

The authors declare no conflicts of interest

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