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Dissolution and bioavailability enhancement of Atorvastatin: Gelucire semi-solid binary system

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ABSTRACT

Atorvastatin (Atv) is one of antihyperlipidimic drugs characterized by limited oral bioavailability due to its low solubility -despite its high permeability- that hinders its full clinical relevance. Herein, we formulated Atv as a binary system with hydrophilic carrier in hard gelatin capsules to enhance the solubility, dissolution rate and subsequently the bioavailability. Gelucire 44/14® and Gelucire 50/13® were selected as the carriers and the prepared formulae were characterized through solubility measurement, FTIR, DSC, and X-RPD analysis. *In vitro* dissolution testing and *in vivo* assessment of the oral bioavailability in New Zealand rabbits were also performed. Atv solubility markedly increased by incorporation with either Gelucire 44/14® or Gelucire 50/13®. FTIR, DSC and X-RPD confirm the successful incorporation of Atv without any chemical alteration or interaction. *In vitro* dissolution showed that up to 85.8% of Atv dissolution within 15 min. Oral bioavailability of the selected formula (C_{max} = 1312 ng/mL and AUC_{0-t} to 11394 ng hr/mL) was higher than Lipitor® (C_{max} = 653 ng/mL and AUC_{0-t} = 4584 ng hr/mL) and higher than free Atv (C_{max} = 527 ng/mL and AUC_{0-t} = 2546 ng hr/mL). These results revealed that Gelucire® formulation has augmented Atv oral bioavailability and this was correlated to the relative improvement of *in vitro* dissolution rate.

1. Introduction

Atorvastatin (Atv) is an antihyperlipidemic drug that plays an important role in the deactivation of HMG-coA reductase (3-hydroxy- 3-methyl-glutaryl-coenzyme A). This enzyme is responsible for internal production of cholesterol through the mevalonate pathway [1]. Lowering the plasma level of cholesterol is continuously associated with a momentous decrease in the risk of cardiovascular diseases [2]. Atorvastatin was initially marketed by Pfizer pharmaceutical company under the brand name Lipitor®. It is currently indicated for primary and secondary prophylaxis against cardiovascular disorders for patients with high cholesterol level of either familial or non-familial reasons [2,3]. Among the other HMG-co A reductase inhibitors, Atv has been recorded as the best-selling one due to its ability to diminish the clogging fatty lining/plague of arterial walls [4]. Although, the cholesterol lowering effect of Atv has been fully investigated and approved, the oral administration of Atv has been associated with low bioavailability (down to only 12%) which decreases its clinical benefits and increases its required daily dose [5]. As with all class II drugs in biopharmaceutical classification system, poor bioavailability of Atv is principally assigned to the low solubility in the gastric fluid.

As a consequence of the aforementioned challenge, various scientists focused on figuring out the optimum delivery for improving oral bioavailability of Atv and the research in this area is still ongoing. Three strategies were developed for this goal. The first strategy aims at increasing the bioavailability through modifying its solid state to enhance the solubility. Modification of solid state is achieved by turning Atv from the crystalline state to amorphous state by spray drying and super critical anti-solvent process [5], reducing its particle size to either micro-size range [6] or nano-size range [7], incorporation within inert water soluble pharmaceutical excipient such polyvinyl pyrrolidone [8], cyclodextrin [9], chitosan [10] and hydroxypropyl methyl cellulose [11]. In addition to, compounding with water soluble emulsifier such as self-emulsifying delivery system [12]. The second strategy is focusing on formulating Atv in gut-retentive sustained release system to retard Atv release for long time and in the same time keeping the formula around the absorption site through either floating in the gastric content [13,14] or muco-adhesion to the buccal cavity [15]. The third strategy mainly depends on loading Atv inside nanoparticles of biodegradable polymers such as poly lactide-*co*-glycolide [16] and poly caprolactone [17], taking advantage of the fact that the nano-size particles are able to reach the blood via the lymphatic circulation through M-cells in the

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payer's patches of the intestine [10].

Amphiphilic pharmaceutical excipients are organic compounds that contain both hydrophilic and lipophilic moieties in their structure [18]. They are extensively used in improving the physicochemical characteristics of active pharmaceutical ingredients, mostly to augment the solubility of sparingly soluble drugs, and clearly found in the pipeline of pharmaceutical production [19]. Gelucires® are contemporarily used amphiphilic excipients. Gelucires® are solid/semisolid mixture of long chain fatty acid esters of polyethylene glycol (mono- and/or di-esters) and glycerides (mono-, di- and/or tri-esters) with free glycerol and polyethylene glycol [18–20]. They are named according to their reported melting temperatures and HLB (hydrophilic lipophilic balance) values. As such Gelucire 50/13® and Gelucire 44/14® have melting temperature 50 °C and 44 °C as well as HLB value of 13 and 14, respectively. Both of Gelucire 50/13® and Gelucire 44/14® are hydrophilic and profoundly used for improving the solubility and *in vivo* absorption of several medicaments including Diazepam [21], Cefuroxime [22], Clotrimazol [23], Praziquantel [24], Curcumin [25], Naproxen [26], Glibenclamide [27], Griseofulvin [28], Erythropoietin [29], and Fenofibrate [30]. Practically, semisolid Gelucires® formulations offer distinctive superiority over previously mentioned approaches [22]. This superiority is attributed mainly to excellent fill weight and content uniformity, in addition to the improved drug stability and controlled release rate through changing HLB value of the used Gelucires® [27]. Gelucires® matrix is also characterized by high *in vivo* biocompatibility and biodegradability due to the absence of impurities [30].

Here, in the present study Atv was formulated as a semi-solid dispersion with Gelucire 44/14® and Gelucire 50/13® and filled into hard gelatin capsules, to enhance its solubility, dissolution rate and bioavailability. We investigated the obtained binary system for the possible interaction between Atv and Gelucires® by FTIR, DSC and X-RPD. Also, the extent of increase in the solubility and dissolution rate were measured *in vitro*. Meantime, we evaluated the *in vivo* bioavailability in comparison with the pure Atv and the Atv tablets existing in the market, using New Zealand rabbits.

2. Material and methods

2.1. Materials

Atorvastatin was thankfully obtained from Jamjoom Pharmaceuticals Co. Ltd (Jeddah, Saudi Arabia). Gelucire 50/13® and Gelucire 44/14® were obtained from Gattefosse' (St. Priest, France), and they have melting temperature around 50.7 and 44.8 °C, respectively. All the further used chemicals were purchased from Sigma-Aldrich (St. Lousi, USA) and handled as obtained without any kind of purification. The water source for all the experiments was the deionized water (Millipore®, 18.2 MΩ cm).

2.2. Preparation of Atorvastatin/Gelucire® semi-solid dispersions

Atorvastatin/Gelucire semi-solid dispersions (Atv/Gel) of different compositions and weight ratios (Table 1) were prepared by fusion method. Accurately weighed amount of Gelucire® was first melted at (50 ± 2 °C) in a suitable porcelain dish and a weighed amount of Atv was added and thoroughly mixed for 5 min by stirring using a magnetic stirrer. The molten Atorvastatin/Gelucire matrix was hand-filled into hard gelatin capsules using preheated stainless steel syringe. The filled capsules were placed in a glass container surrounded by a mixture of ice and salt, to cool rapidly to acquire a congealed solid mass. The capsules were held in -20 °C freezer for 1 h to ensure complete and rapid congealing and then allowed to set in a desiccator at ambient temperature overnight to remove moisture. The mean fill capsules weight and Atv content for each formula were determined to ensure the dose uniformity. For Atv content, each capsule was first dissolved in 50 mL of methanol and then diluted in 1000 mL of deionized water. Sample of 10 mL was then refined by filtration using 0.22 Millipore disposable syringe filter, and Atv content was measured by UV analysis. The measurements were done in triplicate for each formula.

Table 1
Composition, solubility and Gibbs free energy of transfer (ΔG_t) for Atorvastatin formulations using different Gelucires® with various ratios.

Formula code	Atorvastatin (mg)	Gelucire 50/13® (mg)	Gelucire 44/14® (mg)	Solubility (mg/mL)	ΔG_t (kJ/mol) at 37 °C
G41	80	–	400	12.94 ± 0.03	−16.61
G42	80	–	240	4.37 ± 0.03	−13.81
G43	80	–	80	0.67 ± 0.02	−8.97
G51	80	400	–	13.24 ± 0.03	−16.67
G52	80	240	–	6.81 ± 0.03	−14.95
G53	80	80	–	0.58 ± 0.02	−8.63

2.3. Characterization of the prepared Atorvastatin/Gelucire® semi-solid dispersion

2.3.1. Solubility measurements

The increment in the solubility of Atv by solid dispersion with Gelucire® was determined in consonance with the method previously published by Higuchi and Connors [31]. Briefly, an excess amount of Atv and Atv/Gel dispersions were placed in 40 mL scintillation vials to which 20 mL of deionized water was added. The vials were kept under sonication for 1 h at room temperature and then kept at 37 °C in a shaking water bath for 48 h. At the end of the 48 h the content of each vial was filtered using 0.22 Millipore disposable syringe filter and the obtained solutions were diluted and analyzed for Atv by Evolution 201 UV-visible spectrophotometer (Thermo scientific) at 267 nm. The measurements were done in triplicate for each formula.

2.3.2. Fourier transform infrared spectroscopy (FTIR)

Using the Shimadzu IR Prestige infrared spectrometer, FTIR scans were obtained. The spectrometer was attached to a MIRacle attenuated total reflection accessory unit with scanning range of 4000–450 cm^{-1} by mercury cadmium telluride detector. The spectra were collected with a scan number of 32 and at resolution 4 cm^{-1} for all step-scan.

2.3.3. Differential scanning calorimetry (DSC)

Thermal profiles of the prepared solid dispersions were characterized using Q200 differential scanning calorimeter (DSC) supplied with a heat flow sensor and joined via an interface TA Controller TC 15 to a computer. Specimens were enclosed in standard aluminum pans (40 μl) and manually pierced in the lid. A blank pan was used as a reference. Standard indium (melting peak = 156.6 ± 0.3 °C) was used first to calibrate the DSC machine. To get equal thermal history, the measurements were carried out at a heating rate of 10 °C/min at a temperature scan from 0 to 250 °C. Before running the sample, the DSC machine was purged with nitrogen (at a rate of 50 mL/min).

2.3.4. Powder X-ray diffraction analysis (X-RPD)

The powder X-ray diffraction patterns were measured using the Bruker D8-Advance X-ray diffractometer (Bruker, Germany). Scanning was done using Cu Kα radiation at a voltage of 40 kV and 30 mA. The scanned angle was adjusted from 5 to 60° with an accuracy of 0.02 within the measurement range, and the scanning rate was 4°/min.

2.4. Dissolution studies

Using the USP XXVIII paddle apparatus (DT 720 ERWEKA GmbH, Germany), dissolution studies were conducted. Three gelatin capsules containing (80 mg of free Atv or equivalent amount of the prepared formulae in Table 2) were placed in the dissolution medium (900 mL of