ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF DIFFERENT FORMS OF ATORVASTATIN CALCIUM IN DIRECT COMPRESSION TABLET FORMULAS

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Abstract

Atorvastatin, as a synthetic lipid-lowering agent, is an inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG - CoA) reductase which catalyzes the conversion of HMG-CoA to mevalonate, an early rate-limiting step in cholesterol biosynthesis. The bioavailability of atorvastatin is one of the key parameters for its therapeutic use and is dependent on the form of the atorvastatin calcium to be used in the pharmaceutical formulation (amorphous, crystalline or a mixture of both). The patient should take a constant therapeutic daily dose, regardless to the pharmaceutical formulation of the atorvastatin calcium. The major finding of this study was that the addition of buffering and/or alkalizing agent will dramatically increase both, the solubility and dissolution rate of atorvastatin calcium regardless to the form (crystalline, amorphous or a mixture of both) used in the preparation of the direct compression formulas. The results also showed that it was possible to provide therapeutic equivalence of atorvastatin calcium in the pharmaceutical formulation regardless to the form used in the preparation of the direct compression formulas since it was observed that addition of a buffering or alkalizing agent that can provide a pH equal to or greater than (pKa +1), i.e. (pH ≥ 6) can enhance both solubility and dissolution rate of atorvastatin calcium different forms.

Key words: atorvastatin calcium; dissolution rate; alkalinizing agent; buffering agent; direct compression
Introduction

Atorvastatin, as a synthetic lipid-lowering agent, is an inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG - CoA) reductase which catalyzes the conversion of HMG-Co A to mevalonate, an early rate-limiting step in cholesterol biosynthesis [14, 15]. Atorvastatin is currently used as calcium salt for the treatment of hypercholesterolemia [1].

Atorvastatin calcium ([\(R-(R*,R*)\)]-2-(4-fluorophenyl)-\(\beta,\gamma\)-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrol-1-heptanoic acid, hemi-calcium salt). Is a white to off-white crystalline powder that is insoluble in aqueous solution of pH 4 and below; it is very slightly soluble in water and slightly soluble at pH 7.4 phosphate buffers and acetonitrile, slightly soluble in ethanol and freely soluble in methanol. The intestinal permeability of atorvastatin is high at the physiologically intestinal pH (6 – 6.5). However, it is reported that the absolute bioavailability of atorvastatin is 12% after a 40mg oral dose [2].

The empirical formula of atorvastatin calcium is \((C_{33}H_{34}FN_{2}O_{5})_{2}Ca^{2+} \cdot 3H_{2}O\) with a molecular weight of 1209.42. Its structural formula is shown in the figure 1.

![Figure 1](atarvastatin-calcium-structural-formula.png)

Atorvastatin calcium structural formula

The oral bioavailability of atorvastatin is limited by factors such as the membrane permeability, the solubility, the dissolution rate of the drug and so on. Specially, the solubility and the dissolution rate of a sparingly water soluble drug is a critical factor for its oral bioavailability.

Many approaches have been developed in order to improve solubility and to enhance the dissolution rate and oral bioavailability of poorly soluble Atorvastatin like, salt formation, solid dispersion, inclusion complex, micro emulsion and micronization. Physical modifications often aim to increase the surface area, solubility and wettability of the powder particles and are therefore focused on particle size reduction or generation of amorphous states.
Atorvastatin is usually used as its calcium salt since it enables atorvastatin to be conveniently formulated in the pharmaceutical formulations (tablets, capsules, powders) [1].

Atorvastatin can exist in an amorphous form and in many crystalline forms (Form I, Form II, Form III and Form IV) [3].

It is known that the amorphous form in a number of pharmaceutical substances exhibit different dissolution characteristics and bioavailability patterns compared to the crystalline forms [4].

The bioavailability of atorvastatin is one of the key parameters for many therapeutic indications and is dependent on the form of the atorvastatin calcium to be used in the pharmaceutical formulation. Processes for the crystallization and the preparation, respectively, of the amorphous atorvastatin are sometimes difficult to be performed, and as this active substance affords amorphous-crystalline mixtures with a changeable ratio of both forms, that is, crystalline form instead of amorphous form and vice versa. Since there are differences in the solubility among individual atorvastatin forms, particularly emphasizes, also having an indirect impact on its bioavailability, it is very important to ensure uniformity of this drug substance employed in a pharmaceutical formulation of the atorvastatin calcium [5].

The problem of uniformity of atorvastatin calcium may be solved by employing the processes in its finalization which provide constant physical characteristics of the product [5].

The problem occurs when atorvastatin calcium of mutually variable physical characteristics from several different sources is used for the preparation of a pharmaceutical formulation [6]. Optionally the problem can be solved by preparing atorvastatin calcium formulations from a crystalline form only, and from an amorphous form only, before it is incorporated in the formulation, which requires the use of an additional operation resulting in 5 to 10% loss in the final amount of atorvastatin calcium. A further argument for this decision is the fact that atorvastatin calcium is an extremely expensive substance, accordingly all additional operations lead to loss of the active substance which considerably reduces the economical production process.

The patient should be provided with therapeutic equivalent dose regardless to the form of atorvastatin calcium (regarding physical characteristics) incorporated in a pharmaceutical formulation, consequently this work is an attempt to enhance the solubility and dissolution rate of different forms of atorvastatin calcium and enhancing its bioavailability and finally preparing a pharmaceutical solid dosage form (by direct compression).
being constantly therapeutically equivalent irrespective whether the atorvastatin calcium is used in the amorphous and/or crystalline form.

From the chemical structure of atorvastatin we can find that the pKa of atorvastatin’s terminal carboxyl group is (4.5). Therefore, theoretically the solubility and dissolution rate of atorvastatin calcium is markedly improved at pH values equal to or greater than (pKa +1) (i.e. pH in the gastric environment equal or greater than 5.5) [7, 8].

This study involves the preparation of atorvastatin calcium tablet using the direct compression method and a formula containing alkalinizing agent or buffering agent capable of increasing the pH of the gastric environment to a pH level equal to or greater than 5.5.

Materials and methods

Materials

Atorvastatin calcium amorphous/ crystalline and amorphous micronized, (Hangzhou Starshine Pharmaceutical, China); avicel PH 302 (SDI, R&D. Iraq); croscarmellose sodium (Ac–Di-Sol) (FMC BioPolymer, Philadelphia, PA); spray dried lactose (Meggle, Wasserburg, Germany); disodium phosphate Na2HPO4 (Sichuan Youxin Chemical, China); magnesium hydroxide (Shanghai Chemical Industry, China); magnesium stearate (Chris Co Chemical, USA), hydrochloric acid (BDH, England). All organic solvents were of high performance liquid chromatography (HPLC grade) and all the other chemicals were of high purity being of pharmaceutical grade.

Methods

Preparation of Atorvastatin tablets formulas

Atorvastatin tablets were prepared by direct compression method and using the formula listed in table I.

Table I

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amounts (mg), Per Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin calcium Amorphous*</td>
<td>20</td>
</tr>
<tr>
<td>Avicel PH 302</td>
<td>100</td>
</tr>
<tr>
<td>Spray dried Lactose</td>
<td>100</td>
</tr>
<tr>
<td>Disodium Phosphate**</td>
<td>130</td>
</tr>
<tr>
<td>Croscarmellose sodium (Ac-Di-Sol)</td>
<td>25</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>378 mg</strong></td>
</tr>
</tbody>
</table>

*Three forms of Atorvastatin calcium were used; these are (1- Amorphous, 2-Amorphous Micronized and 3- Crystalline) forms.** Used as buffering agent / alkalinizing agent (Magnesium hydroxide)
Preparation of Atorvastatin tablet

Atorvastatin tablets in different formulas were prepared by direct compression in which active ingredients and excipients were sieved. Atorvastatin calcium and spray dried lactose were mixed. Disodium phosphate, Avicel PH 302, Croscarmellose sodium (Ac-Di-Sol) and magnesium stearate were added sequentially to the mixture, mixed and tablet compressed by (MANESTY type F3, single – punch tablet machine, England).

Preparation of film coating

Atorvastatin tablets were prepared by different formulas, were coated with hydroxypropylmethylcellulose (Methocel, HPMC) aqueous coating. Methocel-based coatings in an aqueous base are the most popular coating options. The coating solution was prepared by the following formula as in table II.

Table II

<table>
<thead>
<tr>
<th>Material name</th>
<th>Scale (%), w/v</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxypropyl methylcellulose 2910 15 cps</td>
<td>6.00</td>
<td>Film-forming polymer</td>
</tr>
<tr>
<td>Polyethylene glycol 400</td>
<td>2.00</td>
<td>Plasticizer</td>
</tr>
<tr>
<td>Polyethylene glycol 8000</td>
<td>2.00</td>
<td>Alloying</td>
</tr>
<tr>
<td>Dye Red D&amp;C No. 30 Lake</td>
<td>0.24</td>
<td>Colorant</td>
</tr>
<tr>
<td>Titanium dioxide, special coating grade</td>
<td>2.00</td>
<td>Opacuant</td>
</tr>
<tr>
<td>Water, purified, q.s to q.s</td>
<td>q.s</td>
<td>Vehicle</td>
</tr>
</tbody>
</table>

Procedure: 250 mL of water was placed into a suitable container, and was heated to 60⁰ to 70⁰C. Gently stirring, the hydroxypropylmethylcellulose was dispersed onto the hot water. When the cellulose was moistened, 250 mL of cold water was added quickly and stirred until the dispersion became homogenous. Polyethylene glycol 8000 was dissolved in 50 mL of water, and was added to the step above a suitable sized ball jar was filled with Dye Red No. 30 Lake and titanium dioxide. Water in a sufficient amount was added to cover the pigment and balls and milled overnight. Milled pigments were added to the base solution from the step above, and the volume was made up with cold water.

Physical properties of the prepared tablets

Physical properties of the prepared tablet cores were determined according to the official specifications which include the following tests: Hardness (Breaking strength) using ERWEKA type (TB24A); friability test using Roch friabilator; disintegration time using Manesty tablet disintegrator and weight variation.

Properties of the resulting coated tablets were determined by the following tests: Dimensions (diameter and height) with micrometer; content uniformity, disintegration time, assay of atorvastatin calcium [12].
Dissolution studies

Dissolution studies were performed according to United States Pharmacopoeia (USP XXVIII), paddle method using VK 750d heater/circulator (Vankel, USA). The stirring speed used was 50 rpm, and the temperature was maintained at 37 ± 0.1 °C. Each test was carried out in 900 ml of simulated gastric fluid [11], with a pH 1.2, then 4 ml of aliquot samples were withdrawn in certain time intervals and filtered using 0.11 µm nylon syringe filter. At each sampling time, an equal volume of the test medium was replaced. Filtered samples were appropriately diluted with methanol and assayed for drug concentration by HPLC [11]. The HPLC system consisted of a Waters 2695 Alliance (Milford, MA, USA) separation module attached to a Waters® 2996 photodiode array (PDA) detector. A C18 Inertsil® ODS 3V column (250 mm, 5 µm, GL Sciences Inc., Tokyo, Japan) was used for the analysis. The mobile phase system, consisting of reservoir A (0.01 M ammonium acetate buffer, pH 5.0–acetonitrile; 90:10), reservoir B (0.01 M ammonium acetate buffer, pH 5.0–acetonitrile; 5:95) and reservoir C (0.01 M ammonium acetate buffer, pH 5.0–methanol; 10:90) with a total flow rate of 1 mL/min through the column to elute the analytes. The eluate was monitored by the PDA detector (scan 240 nm) and data integration was carried out by Millennium32 software (version 4) [12, 13].

Results and discussion

Nine atorvastatin calcium direct compression formulations were evaluated officially and noted as AT 1-9 (table III).

Table III
Nine atorvastatin calcium direct compression formulations

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>AT1</th>
<th>AT2</th>
<th>AT3</th>
<th>AT4</th>
<th>AT5</th>
<th>AT6</th>
<th>AT7</th>
<th>AT8</th>
<th>AT9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin calcium amorphous</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Atorvastatin calcium amorphous micronized</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Atorvastatin calcium crystalline</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Avicel PH 302 *</td>
<td>170</td>
<td>100</td>
<td>100</td>
<td>170</td>
<td>100</td>
<td>100</td>
<td>170</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Spray dried Lactose</td>
<td>160</td>
<td>100</td>
<td>100</td>
<td>160</td>
<td>100</td>
<td>100</td>
<td>160</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Disodium Phosphate</td>
<td>---</td>
<td>130</td>
<td>---</td>
<td>130</td>
<td>---</td>
<td>130</td>
<td>---</td>
<td>130</td>
<td>---</td>
</tr>
<tr>
<td>Magnesium hydroxide</td>
<td>---</td>
<td>---</td>
<td>130</td>
<td>---</td>
<td>130</td>
<td>---</td>
<td>130</td>
<td>---</td>
<td>130</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>378</td>
<td>378</td>
<td>378</td>
<td>378</td>
<td>378</td>
<td>378</td>
<td>378</td>
<td>378</td>
<td>378</td>
</tr>
</tbody>
</table>

* The differences were adjusted with an amount of microcrystalline cellulose
**Hardness (Crushing Strength)**

Tablet hardness is a nonspecific term routinely applied to several tablet parameters, including (a) resistance to bending or breaking (b) crushing strength axial or radial (c) impact strength, and (d) resistance to attrition or abrasion.

The mean results of atorvastatin calcium direct compression formulations were $6.6 \pm 0.5$ Kg and these results meet official specification.

**Friability**

Tablet hardness is not an absolute indication of strength since some formulations when compressed into very hard tablet, tend to “cap” on attrition, losing their crown portions. Therefore another measure of tablet strength, which is friability, is often measured. Tablets tend to powder, chip and fragment when handled with lack elegance and influence the consumer acceptance and can create extensively soiled processes in manufacturing areas such as coating and packaging. They can also cause tablet’s weight variation and content uniformity problems.

The mean results of Atorvastatin calcium formulations were $(0.6 \pm 0.2 \%)$ meeting the official requirements.

**Weight variation**

The actual weight of the tablet is determined physically by the diameter of the die and the weight adjustment cam on the tablet machine.

The mean results indicated that no tablet deviated from the average weight by more than $(2.1 \%)$, being accepted officially.

**Disintegration time**

A super disintegrant was incorporated in all tablet formulations in order to fasten the rupture of the tablet, which then will dissolve or release the drug faster than intact tablet.

The mean results disintegration time of the Atorvastatin calcium direct compression formulations was about $(6.3 \pm 0.23)$ minutes and these results met the official specifications.

**Dissolution studies**

All nine Atorvastatin calcium direct compression formulations as in table III have been coated with a round shape, smooth and uniform surface and colored in red.

The dissolution testing of atorvastatin calcium was carried out in a simulated gastric fluid having a pH value of about 1.2 and the concentration of dissolved atorvastatin was then measured at 10 minutes intervals and the pH values were measured at 15 minutes intervals for two times only. Nine different
direct compression formulations were capable of providing different pH values of the aqueous solution of the dissolution medium as seen in the table IV.

The percentage of the drug released from different Atorvastatin calcium direct compression formulations was calculated from samples which were taken in 10 minutes intervals as seen in table V.

**Table IV**

<table>
<thead>
<tr>
<th>pH *</th>
<th>AT1</th>
<th>AT2</th>
<th>AT3</th>
<th>AT4</th>
<th>AT5</th>
<th>AT6</th>
<th>AT7</th>
<th>AT8</th>
<th>AT9</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 15 minutes</td>
<td>1.7</td>
<td>6.09</td>
<td>4.28</td>
<td>1.82</td>
<td>5.88</td>
<td>4.00</td>
<td>1.88</td>
<td>6.71</td>
<td>4.12</td>
</tr>
<tr>
<td>After 30 min</td>
<td>2</td>
<td>8.88</td>
<td>6.78</td>
<td>2.1</td>
<td>8.00</td>
<td>6.08</td>
<td>2.12</td>
<td>8.90</td>
<td>6.22</td>
</tr>
</tbody>
</table>

*One tablet was placed in 900 ml of the simulated gastric fluid in the dissolution vessel

**Table V**

<table>
<thead>
<tr>
<th>Time intervals</th>
<th>AT1</th>
<th>AT2</th>
<th>AT3</th>
<th>AT4</th>
<th>AT5</th>
<th>AT6</th>
<th>AT7</th>
<th>AT8</th>
<th>AT9</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 minutes</td>
<td>40.0</td>
<td>74.1</td>
<td>70.2</td>
<td>55.6</td>
<td>77.2</td>
<td>73.4</td>
<td>32.1</td>
<td>73.9</td>
<td>67.5</td>
</tr>
<tr>
<td>20 minutes</td>
<td>55.1</td>
<td>88.0</td>
<td>77.4</td>
<td>67.8</td>
<td>90.3</td>
<td>80.3</td>
<td>38.5</td>
<td>88.3</td>
<td>74.3</td>
</tr>
<tr>
<td>30 minutes</td>
<td>59.4</td>
<td>90.3</td>
<td>82.1</td>
<td>70.4</td>
<td>95.6</td>
<td>87.2</td>
<td>44.5</td>
<td>91.0</td>
<td>79.1</td>
</tr>
<tr>
<td>40 minutes</td>
<td>62.6</td>
<td>97.8</td>
<td>86.4</td>
<td>73.8</td>
<td>97.3</td>
<td>90.0</td>
<td>47.2</td>
<td>96.4</td>
<td>82.2</td>
</tr>
<tr>
<td>50 minutes</td>
<td>66.8</td>
<td>98.1</td>
<td>90.2</td>
<td>76.0</td>
<td>98.9</td>
<td>94.5</td>
<td>52.0</td>
<td>97.1</td>
<td>88.4</td>
</tr>
<tr>
<td>60 minutes</td>
<td>68.9</td>
<td>99.5</td>
<td>94.0</td>
<td>77.8</td>
<td>99.8</td>
<td>97.2</td>
<td>53.6</td>
<td>98.0</td>
<td>90.1</td>
</tr>
</tbody>
</table>

- For better interpretation of the obtained results, it is evident that all forms of atorvastatin calcium were dissolved better, if the tablet was capable of increasing the pH value to pH \( \geq \), in another word a pH value equal to or greater than (pKa +1) and at this pH all forms of atorvastatin were dissolved better as shown in figure 2.

![Figure 2](image)

**Figure 2**

Percentage of atorvastatin calcium amorphous form release

- The major finding of this study was that the addition of buffering and /or alkalizing agent will dramatically increase both the solubility and dissolution rate of atorvastatin calcium, regardless to which form (crystalline, amorphous or mixture of both) was used in the
preparation of the direct compression formulas. The results also showed that it was possible to provide therapeutic equivalence of atorvastatin calcium in the pharmaceutical formulation regardless to which form (crystalline, amorphous or mixture of both) was used in the preparation of the direct compression formulas since it was observed that addition of a buffering or alkalizing agent that can provide a pH equal to or greater than (pKa +1), i.e. (pH ≥ 6) can enhance both solubility and percentage dissolution of atorvastatin calcium different forms as seen in figure 3.

- It is also evident from the obtained results that the presence of disodium phosphate, as a buffering agent will increase the pH of the medium more effectively than Magnesium hydroxide which was used as alkalizing agent, with significant differences (P ≥ 0.05).
- Without the addition of buffering and/or alkalizing agent there were significant differences in the solubility and dissolution rate between the two major physical forms of atorvastatin calcium (amorphous and crystalline forms), with (P ≥ 0.05) as seen in figure (4).
The current study also included an attempt to enhance the solubility, and then the percentage dissolution rate using special reprocessed form of atorvastatin calcium which was (Atorvastatin calcium amorphous micronized), which had several times larger surface area of the particles compared to non-micronized amorphous form. There are two major outcomes of this study: first, there was a small difference in the percentage of dissolved amorphous and amorphous micronized atorvastatin when formulations contained no buffering and/or alkalizing agent, and second, the difference in the dissolution rate increased to more than (12 – 18 %) when using buffering and/or alkalizing agent.

**Conclusion**

Atorvastatin calcium different forms were dissolved better if the tablet was capable of increasing the pH value to (pH ≥ 6), by the addition of buffering or alkalizing agent at a pH value equal to or greater than (pKa +1), all forms of atorvastatin were dissolved at much faster rate.

The addition of buffering and/or alkalizing agent will dramatically increase both the solubility and dissolution rate of atorvastatin calcium regardless to which form (crystalline, amorphous or mixture of both) was used in the preparation of the direct compression formulas. The results also showed that it was possible to provide therapeutic equivalence of atorvastatin calcium in the pharmaceutical formulation regardless to which form (crystalline, amorphous or mixture of both) was used in the preparation of the direct compression formulas.

The presence of disodium phosphate, as a buffering agent will increase the pH of the medium more effectively than magnesium hydroxide which was used as alkalizing agent, and then enhance both solubility and dissolution rate of atorvastatin calcium different forms.

Atorvastatin calcium amorphous micronized, which has several times larger surface area of the particles compared to non-micronized amorphous form. There are two major outcomes of this study: first, there was a small difference in the percentage of dissolved amorphous and amorphous micronized atorvastatin when formulations contained no buffering and/or alkalizing agent, and second, the difference in the dissolution rate increased to more than (12 – 18 %) when using buffering and/or alkalizing agent.
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