

## Enhancement of Atorvastatin Tablet Dissolution Using Acid Medium

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### Abstract

In this study some generic commercial products of Atorvastatin tablets were evaluated by dissolution test in acid medium by comparing with that of parent drug Lipitor of Pfizer Company. Some of solubilizing agents were studied in formulation of Atorvastatin tablet including; surface active agent and PEG 6000. The most effective factor was the use of PEG6000 in formulation of Atorvastatin tablet which improved the dissolution and the results of dissolution profile of formulated tablet in this work was bioequivalent to that of Lipitor. The quantitative analysis of this work was performed by using reversed phase liquid chromatography and a proper mixture of mobile phase which give a retention time for Atorvastatin about 6 minutes.

### خلاصة

في هذا البحث تم إجراء فحص الانحلالية في الوسط الحامضي على حبوب الاتورفاستاتين المنتجة من قبل عدة معامل دوائية وقد تم إجراء دراسة مقارنة مع قابلية الانحلال لحبوب الاتورفاستاتين والمنتجة من الشركة الأم وهي شركة فايزر (حبوب لبيطور) وفي الوسط الحامضي, كما ان هذا البحث قد احتوى على إجراء تجارب بإضافة مواد تعتبر مساعدة للذوبان مثل صوديوم لوريل سلفيت ومادة بولي ايثيل غلايكول نوع 6000 وقد كانت المادة الاخيرة ذات تأثير فعال على صيغة حبوب الاتورفاستاتين حيث ساعدت في تحسين درجة انحلالية الاتورفاستاتين وأصبح المستحضر المصنع في هذا البحث مكافئ الى المستحضر الاصلي ( لبيطور) ان التحليلات الكمية في هذا البحث قد أجريت باستعمال الطور العكسي للكروماتوغرافيا السائلة وباستعمال خليط مناسب للطبقة المتحركة ليعطي وقت الفصل 6 دقيقة تقريباً.

### Introduction

Atorvastatin calcium is a synthetic lipid-lowering agent. It is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. The absolute bioavailability of atorvastatin is approximately 14%. The low systemic availability is attributed to hepatic first-pass metabolism or mucosa gastrointestinal presystemic clearance<sup>(1)</sup>. The plasma concentrations of Atorvastatin and other related compounds which are metabolized by cytochrome P450 isoenzyme CYP3A4 were increased when these drugs are taken with repeated use of grape fruit juice due to inhibition of this enzyme which is located in the gastro intestinal tract<sup>(2)</sup>. Atorvastatin calcium is practically insoluble in aqueous medium below pH4<sup>(3)</sup>. This physical property of insolubility in water, obviously, will lead to low dissolution in stomach medium. The first study of best dissolution formula which held by Pfizer Co. was carried on gastric medium, and the use of alkalizing agent (Calcium Carbonate) and the surfactant ( sodium lauryl sulphate ) were recommended in formula of Atorvastatin tablet<sup>(4)</sup>. Several studies were reported in attempt to enhance the dissolution of atorvastatin in its solid dosage forms; Complexation of Atorvastatin by Cyclodextrin significantly enhanced its

dissolution, but it is rather tedious procedure<sup>(5)</sup>. Atorvastatin calcium was prepared as a redispersible dry powder for emulsion which was formulated by using dextran as a carrier and poloxamer 188 as a surfactant, its dissolution showed a 2.33 fold increase compared to the pure Atorvastatin calcium powder in vitro gastrointestinal medium<sup>(6)</sup>. In this present study, Lipitor tablet( 20 mg ), the patent drug formulation of Atorvastatin Calcium tablet is tested for dissolution in acid medium and the result was about 92 % dissolved Atorvastatin to the labeled amount. Different generic products of Atorvastatin tablet (commercial products) are evaluated by determination of their dissolution profiles in acidic medium. In addition, some experimental formulations of Atorvastatin Calcium were made in this work and the using of sodium lauryl sulfate in different concentrations and PEG 6000 have been evaluated by their influences on the rate of dissolutions. Determinations of the dissolved amounts of Atorvastatin in acid medium are carried in this work by using a reversed phase HPLC method, prescribed below. Several previous methods of analysis have been used for quantitative determination of Atorvastatin in tablet including spectrophotometry<sup>(7)</sup>, and HPLC method for separation of Atorvastatin and Amlodipine in pharmaceutical formulation<sup>(8)</sup>.

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Received : 9/11/2009

Accepted : 1/6/2010

## Experimental work

### Materials

Atorvastatin Calcium crystalline powder ( supplied by Cadila Healthcare Limited Company ,India ), Sodium Lauryl Sulphate ( Shouguang pharm. Ind.Co.Ltd,China ), poly Ethylene glycol 6000 ( Sasol Germany GmbH. ), potassium dihydrogen phosphate (Reagent grade).Acetonitrile and Methanol (HPLC grade).

### Apparatus

Uv.vis.spectrophotometer , specord 40, analytikjena.HPLC; knauer, Dual piston pump, UV detector and computerized recorder,tablet Dissolution tester USP

### Procedure

6 tablets of each product were tested, one tablet in each of six vessels of the dissolution apparatus of paddle system and 50 RPM ,using 900ml of 0.1M HCL as a medium .the filtered samples were taken at intervals; 10,15,20,25,30,35,40,45 minutes and subjected to HPLC analysis to determine the percent of Atorvastatin Calcium dissolved in medium.

### Method of analysis

An HPLC method for the analysis of Atorvastatin Calcium was carried by using the following chromatographic conditions.

Column: ODS, 25 cm x 4.6 mm

Mobile phase: Acetonitrile: 0.01M potassium Dihydrogen phosphate solution (40:60), adjusted to pH 4.0.with phosphoric acid.

Detection: by U.V at 240 nm. Flow rate: 1.0 ml/minutes.Atorvastatin peak appeared in 6 minutes and the analysis accomplished in 8 minutes (Figure 1)

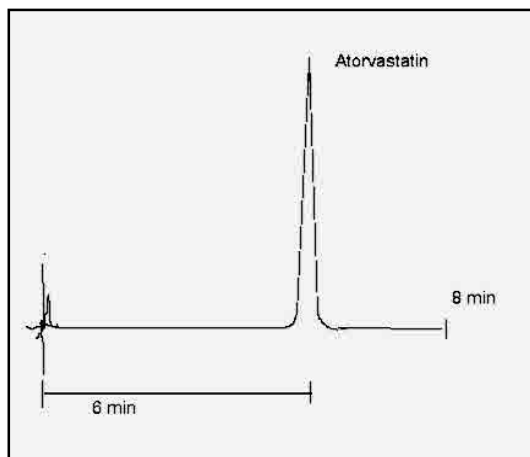


Figure 1: HPLC chromatogram of Atorvastatin tablet in which The peak of Atorvastatin appeared in 6 minutes and the Peaks of the excipients are eluted at the first minute Which indicated that there is no interference with the Assay of Atorvastatin .

The accuracy and precision of this HPLC method were proved since the relationship of different concentrations of Atorvastatin with their peak area ratio have shown a straight line with correlation coefficient of value 0.999.

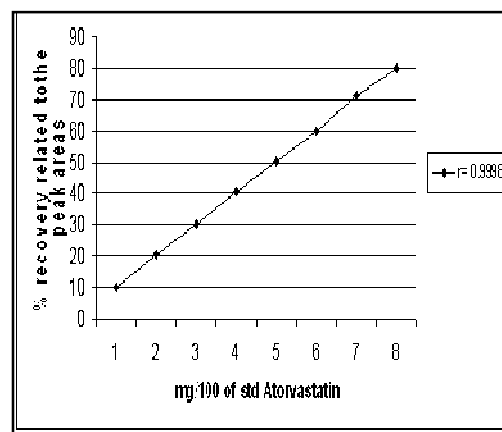


Figure 2: the standard curve of Atorvastatin dilutions with percent recovery peak area Using the reverse d-phase HPLC method.

### Dissolution profile

Three commercial products of Atorvastatin tablet were tested for dissolution in acid medium and compared with that of patent product (Lipitor). Most of the generic formulas of Atorvastatin tablet showed low bioequivalence to Lipitor, (see figure 3 )

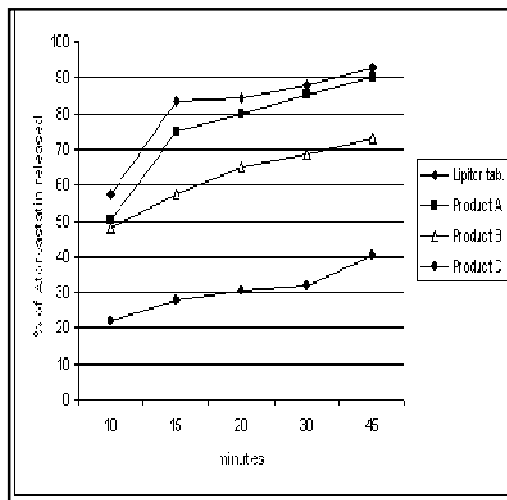
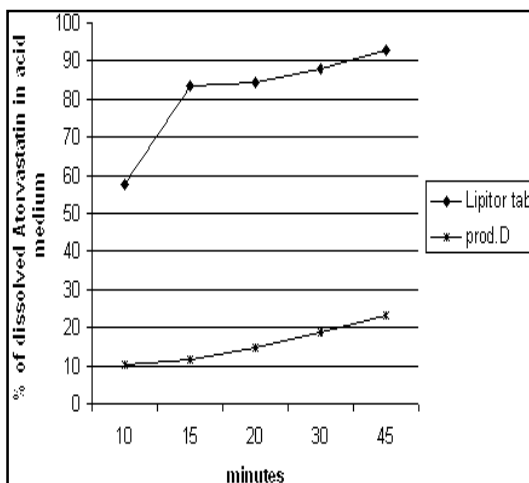


Figure 3 :dissolution profiles of some commercial products of Atorvastatin tablets; where product A ( Avas-20,MICRO Lab.India) was bioequivalent to Lipitor tablet ,however the product B (Atorvatin ,Alfaris Co.Syria) and product C (Atorvast 20,Avanzor,Syria) showed low dissolution .

In my attempt to achieve good Atorvastatin tablet formulation, different experiments were carried in this work considering the acceptable physical properties; hardness, friability and disintegration time in addition to the main requirement; the high dissolution. The first experimental product is termed as (Product D) which contained atorvastatin calcium, calcium carbonate, microcrystalline cellulose, lactose, colloidal silicone dioxide, PVD, magnesium stearate and talc. The dissolution profile of this first formula of product D was too low comparing to Lipitor tablet (figure 4)

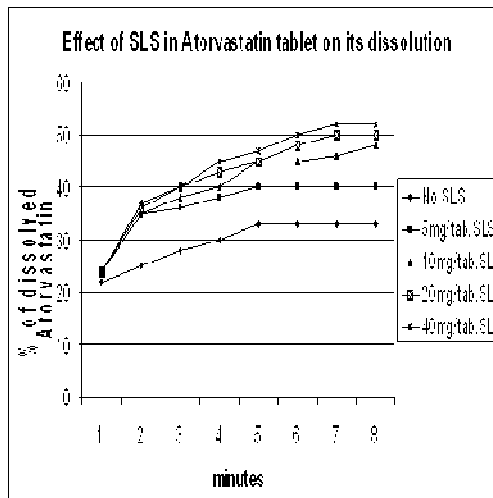


**Figur4: dissolution profile of Product D (the first experimental batch in this work) which showed very low dissolution.**

Therefore, product D formula was subjected to improvement and several experiments were made to evaluate the addition of solubilizing agents

### 1. Effect of surfactant

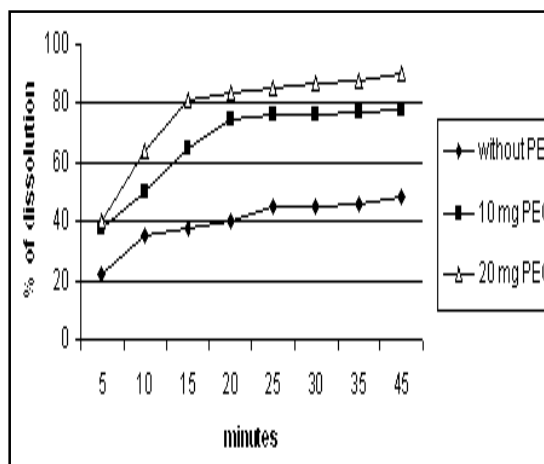
In addition to the ingredients of Atorvastatin tablet mentioned above, different concentrations of sodium lauryl sulphate (SLS) were added in an attempt to increase the dissolution of Atorvastatin. Figure (5) shows that there is significant increase in dissolution of Atorvastatin tablet but it is lower than 80% and there is no significant differences between the added concentrations of 10, 20 and 40 mg of SLS in enhancement of dissolution.



**Figure 5: effect of SLS on dissolution of Atorvastatin tablet in product D.**

### 2. Effect of poly ethylene glycol (PEG 6000)

As it is demonstrated in step 1 the minimum effective concentration of SLS was 10 mg per tablet, in addition to this substance, PEG6000 (finely sieved powder) was incorporated in different concentrations (10 and 20 mg) with the active constituent of Atorvastatin tablet formulations and the dissolution profile for each formula was tested (see figure -6-). The attempts to increase the concentration of PEG6000 more than 20 mg per tablet were failed because the other physical properties of tablet (hardness and friability) were affected.



**Figure 6 : effect of PEG 6000 on dissolution of Atorvastatin tablet in product D**

## **Conclusion**

This study indicated that the formulation of Atorvastatin 20mg tablet with the presence of SLS (10 mg) and PEG6000 (20 mg) per tablet has enhanced the dissolution of Atorvastatin to a value equivalent to that of parent product (Lipitor).

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