A simple isocratic RP-HPLC method for the simultaneous analysis of Metformin hydrochloride and Atorvastatin calcium from bulk drug and combined dosage form

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Abstract: Metformin hydrochloride and Atorvastatin calcium are the preferred duo given in combined dosage form to diabetic people suffering from hypercholesterolemia. A simple and economical RP-HPLC method was developed which would simultaneously quantify Metformin hydrochloride and Atorvastatin calcium. The two drugs were eluted and separated using Symmetry C8 column (150 x 4.6 mm, 3.5 µm, Make: X Terra) as the stationary phase and Methanol-Phosphate buffer (pH 4.5) (55:45, v/v) as the mobile phase. Isocratic mode of elution was used. The flow rate was set at 0.7 mL/min. The detection of the separated analytes was done using the dual wavelength UV detector at λmax of 246 nm. The retention time Metformin hydrochloride was 2.5 mins and that of Atorvastatin calcium was 3.4 mins. The method was linear for Metformin hydrochloride and Atorvastatin calcium in the range of 10-30 µg/ml and 2-6 µg/ml respectively. The average percent recovery for Atorvastatin calcium was 98.8% and for Metformin hydrochloride it was 98.5%. This developed and validated method proved to be sensitive, rapid, precise and accurate. It was successfully applied for the simultaneous estimation of Atorvastatin calcium and Metformin hydrochloride in bulk drugs and pharmaceutical formulations.

Keywords: Isocratic RP-HPLC, Metformin hydrochloride, Atorvastatin calcium, Method development, Method validation

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I. Introduction

Due to hectic routine, improper diet and lack of exercise, diabetes, hypertension, hypercholesterolemia and angina pectoris are the ruling diseases people are suffering from now a days. Atorvastatin calcium (Figure 1A) [calcium (3R,5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-propan-2-ylpyrrol-1-yl]-3,5-dihydroxyheptanoate; trihydrate] is a very potent hyperlipidemic drug. It selectively and competitively inhibits the enzyme 3-hydroxyl 3-methyl glutaryl CoA (HMG-CoA) reductase. This inhibits the conversion of HMG-CoA to mevalonate. Thus, this results in an increase in the low density lipoprotein (LDL) receptor expression on the liver cells and an increase in the uptake and catabolism of LDL and intermediate density lipoproteins (IDL) [1].

Metformin hydrochloride (Figure 1B) [3-(diaminomethylene)-1, l-dimethylguanidine] is a biguanide antidiabetic drug used as a first line treatment of type II diabetes mellitus [2]. Its hypoglycaemic action is the result of its suppression on the hepatic gluconeogenesis and the glucose output from the liver. It also enhances the insulin mediated glucose disposal in muscles and fat [1].

Treatment with Atorvastatin calcium decreases the levels of LDL and hence prevents the risk for stroke, heart attack, and other cardiovascular conditions. However, occurrence of type II diabetes as a side effect is observed in cardiac patients who do not live a healthy lifestyle [3]. Metformin hydrochloride besides its main glucose lowering effect is also proven to have anti-atherosclerotic properties. Studies conducted to determine the effects of the combination therapy of Atorvastatin calcium and Metformin hydrochloride proved significant decrease in atherosclerotic lesion area more effectively than the monotherapy with either of these two medications. The combination therapy also significantly increased the percentage of large high-density lipoprotein sub-fraction [4]. It also reduces the post-glucose loading levels of tumour necrosis factor alpha (TNF-α) compared to Metformin hydrochloride monotherapy. Hence, the Atorvastatin calcium and Metformin

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hydrochloride combination reduces the glucose-induced variations of inflammatory process in patients with diabetes mellitus too [5]. Non-alcoholic fatty liver disease (NAFLD) and type2 diabetes are associated with dyslipidaemia, inflammation and oxidative stress. Atorvastatin calcium- Metformin hydrochloride combination has also been proved to be beneficial in improving liver injury in type2 diabetes with hyperlipidaemia [6].

Atorvastatin calcium and Metformin hydrochloride in a combined dosage form is preferred to increase patient compliance in diabetic patients suffering from hyperlipidaemia. Literature survey revealed various methods for the analysis of Metformin hydrochloride alone [7-9] and combination with other drugs [10, 11]. Atorvastatin calcium has also been analysed alone [12-17] and in combination with various other drugs [18-23] using various analytical techniques. Combination of Atorvastatin calcium, Glimepiride and Metformin hydrochloride has been analysed by HPLC [24, 25], LC-MS/MS [26] and HPTLC [27, 28]. Glimepiride is known to be given to diabetic patients who are inadequately treated with Metformin hydrochloride. Atorvastatin calcium and Metformin hydrochloride have been analysed along with Telmisartan [29] and Sitagliptin [30] by UV spectroscopy and HPLC method respectively.

A fixed dose combination of Atorvastatin calcium 10mg and Metformin hydrochloride 500mg SR has been proven efficient in patients with diabetic dyslipidaemia [31]. Combination of Metformin hydrochloride and Atorvastatin calcium alone has shown a substantial reduction in major cardiovascular events in patients with both Type 2 diabetes and coronary artery disease [4, 5 and 6].

The aim of our study was to develop a rapid and sensitive method for the simultaneous estimation of Atorvastatin calcium and Metformin hydrochloride from bulk drugs and from their combined dosage forms. The method was also validated to prove its precision and accuracy. The retention time (Rt) of Metformin hydrochloride and Atorvastatin calcium and hence the run time in the previous methods, where these drugs were analysed along with Glimepiride and Sitagliptin by HPLC was more [24, 25 and 30]. Since the combination on which we were working was Metformin hydrochloride and Atorvastatin calcium alone, our aim was to have shorter retention time and hence a reduced run time by using RP-HPLC as the method for analysis. This would make their analysis more economical.

II. Materials And Experimental Conditions

2.1 Chemicals, Reagents and Materials:

Atorvastatin calcium API and Metformin hydrochloride API were obtained as gift samples from Mylan India Ltd, Bollaram, Hyderabad, India. Xmeter 10 mg/500 mg tablets SR of Glenmark Pharmaceuticals Ltd. were purchased from the local pharmacy. HPLC grade Methanol was purchased from J.T. Baker (Philipsburg, USA). Water for chromatography (HPLC grade) was purchased from Merck KGaA (Darmstadt, Germany). Potassium dihydrogen orthophosphate (AR grade), sodium hydroxide (AR grade) and orthophosphoric acid (AR grade) used for the preparation of Buffer pH 4.5 were purchased from SD fine chemicals (Mumbai, India).

2.2 Instrumentation:

Waters High Performance Liquid Chromatography (HPLC) system equipped with Waters 2695 separation module and Waters 2487 dual absorbance detector (DAD). Empower 2 software was used for the integration of the response of the analytes. Mettler Toledo pH meter was used to check the pH of the mobile phase buffer. Analytical balance and microbalance both of the make Mettler Toledo were used during the analysis. Leelasonic-200 bath sonicator was used for degassing the mobile phase and dissolving the solute in the solvent.

2.3 Chromatographic parameters:

Symmetry C8 column (4.6 x 150 mm, 3.5µm, Make: XTerra) was used as the stationary phase. Mobile phase consisting of Methanol – Phosphate buffer pH 4.5 (55:45, v/v) was used to elute the analytes. The wavelength used for detection was 246 nm. The column was maintained at ambient temperature. The flow rate was set at 0.7 mL/min. An injection volume of 20 µL was fixed. The temperature of the auto-sampler was maintained at 10°C.

2.4 Preparation of Solutions:

2.4.1 Preparation of Phosphate buffer (pH 4.5):

Potassium dihydrogen phosphate (7 gms) was dissolved and diluted to 1000 mL with HPLC water. It was adjusted to pH 4.5 with orthophosphoric acid.

2.4.2 Preparation of mobile phase:

Methanol was mixed with Buffer pH 4.5 in the ratio 55:45, v/v. This was then degassed in ultrasonic water bath for 5 minutes and filtered through a 0.45 µm filter. The mobile phase was used as the diluent.
2.4.3 Preparation of Standard solution:
Metformin hydrochloride stock solution (1 mg/mL) and Atorvastatin calcium stock solution (0.1 mg/mL) was prepared using the diluent. Further using the above stock solutions a standard solution containing 20 µg/mL of Metformin hydrochloride and 4 µg/mL of Atorvastatin calcium was prepared using the diluent.

2.4.4 Preparation of Sample solution:
Ten tablets of Xmetor-10 mg/500 mg tablets SR were weighed and crushed. Tablet powder equivalent to 10 mg of Atorvastatin calcium and 500 mg of Metformin hydrochloride was dissolved and diluted with the diluent to produce 4 µg/mL of Atorvastatin calcium and 20 µg/mL of Metformin hydrochloride.

2.5 Chromatographic Procedure:
A volume of 20 µL of the standard solutions and sample solutions of Metformin hydrochloride and Atorvastatin calcium were injected into the chromatographic system. The drugs were eluted using the above chromatographic parameters. The peak areas of Metformin hydrochloride and Atorvastatin calcium were measured and the percent standard deviation was calculated.

III. Method Validation

The method was validated as per the ICHQ2 (R1) guidelines [32].

3.1 System suitability:
System suitability for the method was determined by analysing six replicate injections of the Standard solution containing 20 µg/mL of Metformin hydrochloride and 4 µg/mL of Atorvastatin calcium.

3.2 Specificity:
The Specificity of the method for Metformin hydrochloride and Atorvastatin calcium was checked by injecting the mobile phase (also used as the diluent), placebo solution, Metformin hydrochloride (20 µg/mL) solution, Atorvastatin calcium (4 µg/mL) and the standard solution containing Metformin hydrochloride and Atorvastatin calcium. The chromatograms of all of the above were compared.

3.3 Limit of Detection (LOD) and Limit of Quantitation (LOQ):
LOD and LOQ were determined by the Signal to Noise (S/N) ratio method.

3.3.1 Limit of Detection:
A concentration of 19 ng/ml of Metformin hydrochloride solution and 20 ng/ml of Atorvastatin calcium solution was prepared from their respective stock solutions using the diluent. Baseline noise from the blank was obtained. The signal to noise ratio was calculated.

3.3.2 Limit of Quantitation:
A concentration of 60 ng/ml of Metformin hydrochloride solution and 60 ng/ml of Atorvastatin calcium solution was prepared from their respective stock solutions using the diluent. Baseline noise from the blank was obtained. The signal to noise ratio was calculated.

3.4 Linearity and Range:
The Linearity of the method was studied at five different concentration levels. Solutions of range of concentrations from 10 - 30 µg/mL of Metformin hydrochloride and 2 - 6 µg/mL of Atorvastatin calcium were analysed by the above developed method and their peak areas were determined. The calibration curves of peak area versus concentration (µg/mL) were plotted for each of the above drugs. The linear regression equation and the coefficient of correlation were determined for Metformin hydrochloride and Atorvastatin calcium.

3.5 Precision:
The precision of the method was evaluated by determining the System precision (Repeatability), Method precision and Intermediate precision (Ruggedness). For system precision a standard solution containing 20 µg/mL of Metformin hydrochloride and 4 µg/mL of Atorvastatin calcium was injected six times. While the method precision was evaluated by preparing six different sample solutions containing the same above concentration of the two drugs and injecting twice each of these solutions. For intermediate precision, the same above procedure was repeated by another analyst on another HPLC system and using another column.

3.6 Accuracy:
The accuracy of the method was determined by performing the recovery studies at 80%, 100% and 120% of the target assay concentration. The recovery studies were done by the standard addition method. In
three volumetric flasks, sample solution equivalent to 100% assay concentration was taken. To this 80%, 100% and 120% of the target assay concentration of the standard solution was added. The % Recovery was calculated.

3.7 Robustness:
To determine the robustness of the method, small deliberate changes in the flow rate, mobile phase composition and the column temperature were made.

3.8 Stability of Solution:
The Stability of the standard solutions and sample solution was determined at room temperature (~ 25°C) and at 10°C at 0 hour, 24 hours and 48 hours after preparation.

IV. Assay Of The Marketed Formulation
Ten Ten Xmetor- 10 mg/500 mg tablets SR were weighed and the average weight was determined. The tablets were crushed to prepare a homogeneous mixture. The sample solutions were prepared in duplicate using the above mentioned procedure. The standard mixture solution was also prepared. A volume of 20 µl of the standard mixture was injected six times. The two sample solutions were injected (20 µl volume) in duplicate. The peak areas were determined and the % Assay was calculated.

Calculations
\[
\% \text{ Assay} = \frac{\text{Sample Area \times wt. of Std} \times \text{Dilution of Sample} \times \% \text{ purity of Std}}{\text{Avg. wt} \times 100}
\]

V. Results And Discussion

5.1 Optimisation of the Method:
Metformin hydrochloride has a low logP value (log10 of the distribution coefficient between 1-octanol and water) of −1.43 [33]. The log P value of Atorvastatin calcium is 5.6 [34]. Metformin hydrochloride is freely soluble in water and methanol, slightly soluble in ethanol and almost insoluble in acetone, ether, and chloroform [33]. Atorvastatin calcium is very slightly soluble in distilled water, acetonitrile; slightly soluble in ethanol and freely soluble in methanol. It is practically insoluble in aqueous solutions of pH 4 and below [34].

Reversed phase chromatography was chosen to simultaneously analyse the two drugs. Wherein, the two drugs because of their chemical nature would easily be eluted along with the polar mobile phase. This will result in better peak shapes and shorter run times.

Methanol and Acetonitrile were both tried as organic modifiers in the mobile phase. Combinations of Methanol along with buffers of various pH were experimented with to get resolved peaks with good peak shape and less run time. Similarly, combination of acetonitrile with buffers 3-7 were tried with. Atorvastatin calcium showed more solubility in methanol than in acetonitrile. Methanol is known to be inexpensive and less toxic than acetonitrile. Using methanol during the optimisation of the mobile phase gave a good resolution, good peak shape and a shorter run time. Methanol: Buffer pH 4.5 (55:45, v/v) was finalised as the mobile phase. The mobile phase was itself used as the diluent.

Analytical C8 and C18 columns of various makes like Inertsil, Zorbax, Hypersil, Kromasil and Symmetry were tried with. The column dimension of 4.6 x 250 mm with 5µ particle size was tried, but the results were not satisfactory. There was an increase in the retention time of the analytes and the peak shape of Metformin hydrochloride was not good. To shorten the retention time and to increase the efficiency of the column, Symmetry C8 column (4.6 x 150 mm, 3.5 µ) was chosen. The column gave good results. The Rt of the analytes were less, the resolution between them was high and the peak shape of both the analytes was good and symmetrical.

The lambda max (λ max) of Metformin hydrochloride in methanol determined by UV spectroscopic measurement was found to be 240 nm. While that of Atorvastatin calcium was 246 nm. The overlaid spectral measurement of the above two drugs was done. At 246 nm wavelength, maximum sensitivity of the method was observed. Hence the simultaneous analysis of Metformin hydrochloride and Atorvastatin calcium was done at 246 nm.

5.2 Method Validation:
In the test for system suitability, it was observed that the theoretical plate count is more than 2000, the resolution is more than 1.5 and the tailing factor is less than 2. The method was suitable with the HPLC system, the electronics and the Empower 2 software, as proved by the system suitability test (Results are shown in Table 1). No peaks of the diluent (mobile phase) and the placebo were seen at the Rt of the two analytes. Hence the method was specific. Figure2A, Figure 2B and Figure 3 represent the chromatograms of the diluent (mobile phase), placebo and the standard mixture solution of Metformin hydrochloride and Atorvastatin calcium respectively. The calibration curves of Metformin hydrochloride (y = 258722x) and Atorvastatin calcium (y =
695010x + 25344) showed good linearity within the tested concentration range of 10-30 µg/ml for Metformin hydrochloride and 2-6 µg/ml for Atorvastatin calcium. The coefficient of correlation (r) for Metformin hydrochloride was found to be 0.9993, while that for Atorvastatin calcium was 0.9992. Hence, the Beer-Lambert’s law was obeyed. The calibration curves of Metformin hydrochloride and Atorvastatin calcium are shown in Figure 4.

The % CV in system precision, method precision and intermediate precision test was less than 2%, hence the method was proved to be precise (results are given in Table 2). Since the precision test performed by another analyst, using another column on another system (intermediate precision) gave % CV less than 2%, the method proved to be rugged. The mean percent recovery for Metformin hydrochloride and Atorvastatin calcium was found to be 98.5% and 98.7%. Hence the method was accurate (results are given in Table 3). The LOD and LOQ for Metformin hydrochloride was 19ng/mL and 60ng/mL respectively. While the LOD and LOQ for Atorvastatin calcium was 20ng/mL and 60ng/mL respectively. Therefore, the method was very sensitive.

The method was robust on variation of the flow rate by ±10%. The method was also found to be robust on variation in the organic composition of the mobile phase by 10%.

Stability of the standard and sample solutions was checked by determining the % CV of the peak areas of the above solutions at 0 hour, 24 hours and 48 hours. The % CV of peak areas of the standard solution of Metformin hydrochloride at 10 ºC and at R.T. was found to be 0.82 and 1.66 respectively. While for the % CV of peak areas of the sample solutions of Metformin hydrochloride at 10 ºC and R.T. was found to be 1.09 and 2.25 respectively. For the standard solution of Atorvastatin calcium, the % CV for the peak areas of solutions stored at 10 ºC and R.T. was found to be 0.8 and 1.22 respectively. While for the sample solutions of Atorvastatin calcium, the % CV of the peak areas of solutions stored at 10 ºC and R.T. was found to be 0.51 and 1.21 respectively. Extra peaks, splitting of peaks and decrease in peak area was also checked for. The stability of the solutions at 10 ºC proved to be better than at R.T. The % CV of the peak areas of standards and samples of both the drugs stored at R.T. was more than for the same solutions stored at 10 ºC, but they were less than 2%(except for the samples solution of Metformin hydrochloride which was stored at R.T., whose % CV was more than 2%). Hence the standard and sample solutions of Metformin hydrochloride and Atorvastatin calcium should be stored in the refrigerator at around 10 ºC and the temperature of the auto-sampler should also be maintained at 10 ºC.

VI. Conclusion
The proposed isocratic RP-HPLC method for the simultaneous analysis of Metformin hydrochloride and Atorvastatin calcium proved to be rapid, sensitive, precise and accurate. The use of methanol in mobile phase gave better peak shape and shorter run time. Hence the method is more economical. The method can be used for the routine analysis of the above anti-diabetic and hyperlipidemic drug combination from bulk drugs and combined dosage form without their prior separation. It can also be used for bioequivalence studies by companies producing generic products of combination of Metformin hydrochloride and Atorvastatin calcium.

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Figure 1: Chemical structures of A) Atorvastatin calcium and B) Metformin hydrochloride

Figure 2: Chromatogram of A) Diluent and B) Placebo

Figure 3: Chromatogram of the Standard mixture solution of Metformin hydrochloride and Atorvastatin calcium

Figure 4: Calibration curves of (A) Metformin hydrochloride and (B) Atorvastatin calcium.
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Table 1: System suitability test results:

<table>
<thead>
<tr>
<th>ANALYTE</th>
<th>RETENTION TIME (min)</th>
<th>MEAN AREA</th>
<th>USP PLATE COUNT</th>
<th>RESOLUTION</th>
<th>USP TAILING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin hydrochloride</td>
<td>2.5</td>
<td>5537427</td>
<td>4236</td>
<td>-----</td>
<td>1.1</td>
</tr>
<tr>
<td>Atorvastatin calcium</td>
<td>3.4</td>
<td>2645338</td>
<td>4355</td>
<td>3.2</td>
<td>1.1</td>
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Table 2: Results for the Precision studies for Metformin hydrochloride and Atorvastatin calcium:

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<th>System Precision</th>
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<th>Atorvastatin calcium</th>
<th>Method Precision</th>
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<th>Atorvastatin calcium</th>
<th>Intermediate Precision</th>
<th>Metformin hydrochloride</th>
<th>Atorvastatin calcium</th>
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</thead>
<tbody>
<tr>
<td>Mean area</td>
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<td>5434118</td>
<td>2752978</td>
<td>5257650</td>
<td>2774987</td>
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</tr>
<tr>
<td>S.D</td>
<td>20357.3</td>
<td>5215.78</td>
<td>24139.49</td>
<td>23768.69</td>
<td>45206.4</td>
<td>22806.9</td>
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<td>% CV</td>
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<td>0.45</td>
<td>0.86</td>
<td>0.86</td>
<td>0.82</td>
<td>0.86</td>
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Table 3: Accuracy results of Metformin hydrochloride and Atorvastatin calcium:

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<tr>
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<th>Amount found (mg)</th>
<th>% Recovery</th>
<th>Mean Recovery</th>
<th>Amount added (mg)</th>
<th>Amount found (mg)</th>
<th>% Recovery</th>
<th>Mean Recovery</th>
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<td>98.5%</td>
<td>4.90</td>
<td>4.81</td>
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<td>9.80</td>
<td>9.77</td>
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<td>14.8</td>
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