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Drug-Drug Interaction Study of Atorvastatin Calcium with Metformin HCl And Multivitamin Tablets using *In vitro* Dissolution Test

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Abstract

Atorvastatin calcium is a synthetic lipid lowering drug. Now days it is being highly used for cardiovascular disease, hypercholesterolemia and many other diseases. Now a day's most of the patient suffers from both diabetes and hypercholesterolemia. Therefore, physicians prescribe Metformin HCl and Atorvastatin at the same time. The potential drug-drug interaction (DDI) exists whenever two or more drugs are co-administered. The objective of this work is to compare the differences in dissolution behavior of Atorvastatin calcium tablets alone and combination of Atorvastatin with Metformin HCl and Multivitamin tablets to assess the drug – drug interaction. The other drugs prescribed with Atorvastatin at the same time, selected by sorting out prescriptions of different cardiovascular patients from different hospitals. Some prescriptions were selected where a patient has to administer Atorvastatin with Metformin HCl and Multivitamin tablets. The *in vitro* dissolution of Atorvastatin calcium alone and combination with Metformin HCl and Multivitamin tablets were performed using USP dissolution apparatus II and pH 6.8 phosphate buffer solutions. The % dissolution of Atorvastatin calcium alone and combination were compared and determined there is an synergistic activity in combination of Atorvastatin calcium tablets with Metformin HCl tablets and Multivitamin tablets. Therefore the effect of above mentioned drugs simultaneously in combination increases the % dissolution of Atorvastatin thus increasing the bioavailability even more than usual.

Keywords: Hypercholesterolemia, Diabetes, Drug-Drug interaction, Synergistic activity and *In vitro* dissolution

INTRODUCTION

Atorvastatin calcium is a synthetic lipid lowering drug. Now days it is being highly used for cardiovascular disease, hypercholesterolemia and many other diseases. Atorvastatin is an inhibitor of 3- hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase[1]. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate limiting step in cholesterol biosynthesis. Atorvastatin is used to lower cholesterol and triglyceride levels in the blood[2]. Metformin Hydrocloride is a biguanide, which used orally in hyperglycemic patients. Nowadays it is widely used in the management and control of non-insulin dependent diabetes mellitus (NIDDM). The oral bioavailability of metformin is 50 – 60%. It is freely soluble in water and has low permeability to cell membranes[3].

Now a day's most of the patient suffers from both diabetes and hypercholesterolemia. Therefore, physicians prescribe Metformin HCl and Atorvastatin at the same time. The potential drug-drug interaction (DDI) exists whenever two or more drugs are co-administered. Drug-drug interactions may be beneficial or harmful. Harmful drug-drug interactions are important as they cause adverse drug reactions (ADR) requiring hospitalization. DDI can determine from the *in vitro* dissolution studies, the dissolution rate can vary when drug – drug interaction occurred[4]. *In vitro* dissolution is a test used to characterize the dissolution properties of the active drug from a dosage formulation. Drugs administered orally in solid dosage forms, such as tablet or capsules, must dissolve in the contents of the gastrointestinal tract before drug absorption can occur[5].

In this study to determine the dissolution rate of Atorvastatin, when it given alone and when it is given combination of Atorvastatin Calcium with Metformin HCl and Multivitamin. From the dissolution data to determine drug –drug interaction is occurring or not.

MATERIALS

Atorvastatin Calcium was purchased from Coastal Chemical Limited, Visakhapatnam, Atorvastatin Calcium, Metformin HCl and Multivitamin tablets were purchased from local market vijayawada, NaOH from S.D. Fine Chem. Ltd, Mumbai, KH_2PO_4 was obtained from Qualigens Fine chem, Mumbai and all other ingredients used were of analytical grade.

EXPERIMENTAL METHODS

Identification of Pure Drug:

FTIR spectroscopy was used for identification of pure drug Atorvastatin Calcium[6].

Determination of λ_{max}:

Preparation of Stock Solution: An accurately weighed 10 mg of Atorvastatin Calcium was transferred in a 100 ml volumetric flask. To the flask phosphate buffer was added in small proportion so as to dissolve Atorvastatin Calcium. The volume was made up to 100 ml with phosphate buffer pH 6.8 to get a concentration of 100 µg/ml.

Determination of λ_{max}: 20 µg/ml solution of Atorvastatin Calcium was prepared in dilution. The resulting solution was scanned in UV-Vis spectrophotometer from 400- 200 nm to determine the λ_{max}[7].

Calibration of Standard Curve:

Accurately weighed 100 mg of Atorvastatin Calcium was dissolved in 100 ml of pH 6.8 phosphate buffer solution. The resultant solutions were having concentration of 1000 µg/ml (1 mg/ml). 1 ml of this solution was further diluted up to 100 ml with 6.8 pH phosphate buffer to give a

solution of Concentrations 10 µg/ml. This resultant solution was used as standard stock solution. Appropriate aliquots were pippeted out from the standard stock solution in to a series of 10 ml volumetric flasks. The volume was made up to the mark with 6.8 pH phosphate buffer to get a set of solutions having the concentration range of 0, 1, 3, 5, 7 and 9 µg/ml for Atorvastatin Calcium. Absorbance of the above solutions was measured at 242 nm, a calibration curve of absorbance against concentration was plotted and the regression equation and correlation coefficient was determined[7].

Predecting Drug Interaction By *Invitro* Dissolution

The Atorvastatin Calcium, Metformin HCl and Multivitamin tablets were procured from the local market in Vijayawada[8]. Atorvastatin Calcium tablets contained label strength of 20 mg and Metformin HCl tablets contained label strength of 500 mg. The drug – drug interaction was determined through the evaluation of *in vitro* dissolution of Atorvastatin Calcium tablets alone and combination with Metformin HCl and Multivitamin tablets. The dissolution test was performed within tablets expiration dates. The strength and other details were given in Table 1.

Table-1: Composition of Commercial Tablets

Brand Name	Label strength (mg)	Manufacturer	Batch No.	Mfg – Exp Date
Lipikind	Atorvastatin Calcium 20	Mankind Pharma Limited	A2ACR004	2018-2020
Okamet	Metformin HCl 500	Cipla Limited	E770732	2017-2020
ISITONE	Multivitamins	ISIKA Pharma, limited	T-1718227	2018-2020

***In vitro* Dissolution Test:** The rotating paddle method (USP apparatus II) was used to study the drug release from Atorvastatin Calcium tablets alone and in combination of Metformin HCl and Multivitamin tablets[9]. The dissolution medium consisted of 900 ml of pH 6.8 phosphate buffer. The release was performed at $37^0C \pm 0.5^0C$, at a rotational speed of 75 rpm. 10 ml samples were withdrawn at intervals over the period of 1 hr and the volume was replaced with fresh medium. The samples were filtered through whatman filter paper and analyzed for Atorvastatin Calcium after appropriate dilution by UV spectrophotometer at 242 nm. The percentage of drug released is calculated using the given formula[10].

RESULTS AND DISCUSSION

Identification of Pure Drug:

FT-IR spectroscopy was used to determine the functional group present in the pure drug sample. Spectra of Atorvastatin Calcium had shown characteristic peak at 2933.74 cm^{-1}(C-H – stretching), 1314.81 cm^{-1}(C-N – stretching), 3061.91 cm^{-1} (C-HO - stretching alcoholic group), 1568.04 cm^{-1} (C=O – stretching am idic group), 3382.29 cm^{-1} (N-H - stretching), 1651.82 cm^{-1} (C=C - bending), 752.30 cm^{-1}, 691.50 cm^{-1} (C-F- stretching), 1157.10 cm^{-1} (O-H- bending).

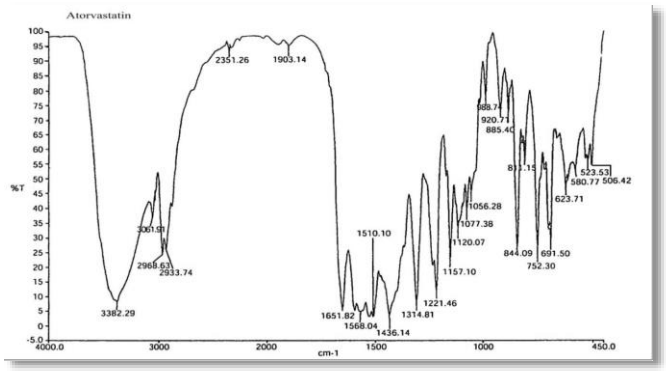

Fig-1: IR Spectra of Pure Atorvastatin Calcium

Determination of λmax:

The 20 µg/ml Atorvastatin Calcium solution was scanned in UV-Vis spectrophotometer from 400- 200 nm to determine the λmax. The λmax was found to be at 242 nm, so the calibration curve of Atorvastatin Calcium was developed at this wavelength.

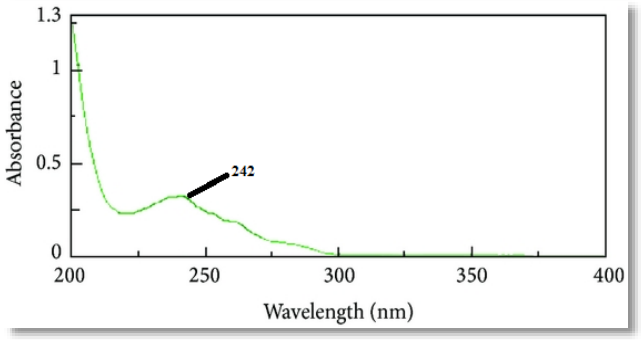

Figure-2: UV Spectra of Atorvastatin Calcium

Standard Curve of Atorvastatin Calcium:

The standard curve of Atorvastatin Calcium was done by using pH 6.8 PBS as the medium. The absorbances of solutions were examined under UV- spectrophotometer at an absorption maximum of 242 nm. The standard graph was constructed by taking the absorbance on Y-axis and concentrations on X-axis. The standard curve of Atorvastatin Calcium in pH 6.8 PBS had showed in Fig.13. Drug concentration and absorbance followed linear relationship the curve obeyed Beer-Lambert's law and the correlation coefficient value (R^2) is 0.992.

Table-2: Standard Calibration Curve of Atorvastatin Calcium

S.NO	Concentration (µg/ml)	Absorbance at 242 nm
1.	0	0.0
2.	1	0.049
3.	3	0.154
4.	5	0.238
5.	7	0.338
6.	9	0.485

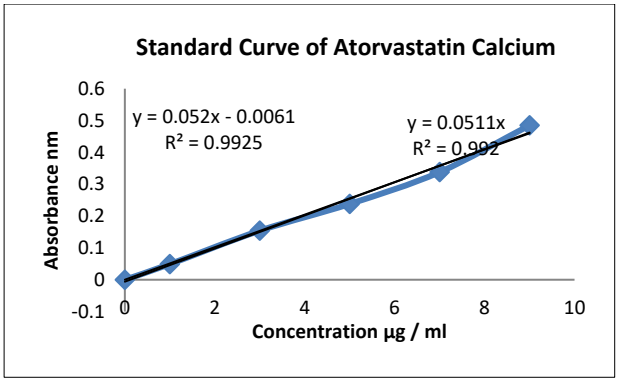

Figure-3: Standard Calibration Curve of Atorvastatin Calcium in pH 6.8 PBS

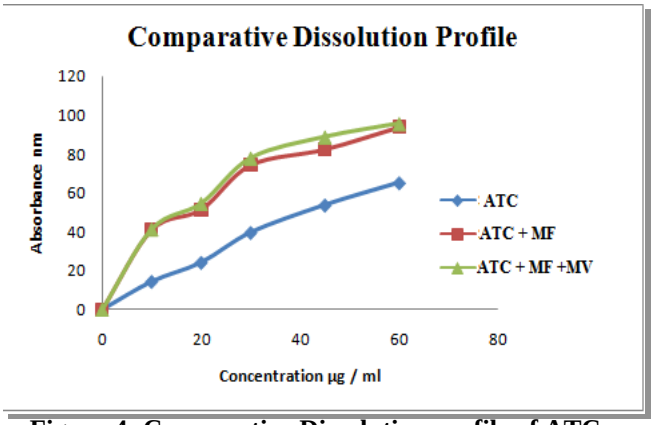

Figure-4: Comparative Dissolution profile of ATC, ATC + MF & ATC + MF + MV

Predecting Drug Interaction by *Invitro* Dissolution

The prescription of different cardiovascular patients from different hospitals was sorting out and some prescriptions were selected where a patient has to administer Atorvastatin with Metformin HCl and Multivitamin tablets. The drug - drug interaction of Atorvastatin calcium (Lipikind®) in combination with Metformin HCl (Okamet®) and Multivitamin tablets (Isitone®) were determined using comparative *in vitro* dissolution study.

Comparative Dissolution Studies: The *in vitro* dissolution of Atorvastatin calcium alone and combination with Metformin HCl and Multivitamin tablets were performed using USP dissolution apparatus II and pH 6.8 phosphate buffer solutions. When Atorvastatin calcium was tested alone the percentage dissolved after 60 minutes was found to be 65.16 %. When Atorvastatin calcium was tested in combination with Metformin HCl and combination with Metformin HCl and Multivitamin tablets the % dissolved after 60 minutes was found to be 93.72 % & 95.56 % respectively. The results of dissolution explained there is an synergistic activity in combination of Atorvastatin calcium tablets with Metformin HCl tablets and Multivitamin tablets. This effect may occurred due to form complex with other drugs or substances as a drug- drug interaction. Therefore the effect of above mentioned drugs simultaneously in combination increases the percentage dissolution of Atorvastatin thus increasing the bioavailability even more than usual. *In vivo* and large scale studies are highly recommended because as a result of interaction Atorvastatin release was increased.

Table-3: % drug release from ATC alone, ATC + MF and ATC + MF + MV

Time (min)	Average Cumulative % Drug Release		
	ATC Alone	ATC + MF	ATC + MF + MV
10	14.32	40.93	41.25
20	24.14	51.37	54.47
30	39.53	74.25	77.81
45	53.68	82.33	88.69
60	65.16	93.72	95.56

Where ATC – Atorvastatin Calcium Tablets
MF – Metformin HCl Tablets
MV – Multivitamin Tablets

CONCLUSION

In this study, the percentage dissolution of Atorvastatin calcium alone and combination were compared and observed there is a synergistic activity in combination of Atorvastatin calcium with Metformin HCL and Multivitamin tablets. This effect may occurred due to form complex with other drugs or substances. The synergistic effect of above mentioned combination may increases bioavailability and may decrease dose of Atorvastatin calcium as compared to administering alone. Therefore, the co-administration of these drugs was safe.

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