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"PHYSICOCHEMICAL PROPERTIES OF ATORVASTATIN CALCIUM AND ITS COMPATIBILITY WITH VARIOUS INACTIVE INGREDIENTS"

Pavan Kumar Gangavarapu*

Senior Director, Regulatory Affairs, 21 Colonial Dr. Piscataway, New Jersey, USA.

***Corresponding Author: Dr. Pavan Kumar Gangavarapu**
Senior Director, Regulatory Affairs, 21 Colonial Dr. Piscataway, New Jersey, USA.

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ABSTRACT
The present study aimed to understand the physicochemical properties of Atorvastatin Calcium and its compatibility with various inactive ingredients (excipients) which are suitable to formulate Tablet dosage form. Each excipient was individually mixed with Atorvastatin Calcium (API) and this blend was kept in a closed transparent glass vial at 40°C/75% RH for four weeks. The samples were analyzed for Related Compounds to determine the drug excipient's compatibility.

KEYWORDS: Drug Substance, Compatibility, Physicochemical Properties, Related Compounds, Stability, Pre-formulation.

INTRODUCTION

Due to the growing complexity of drug substances and formulations, developing a quality drug product and a process that manufactures it in a reproducible manner becomes increasingly challenging and costly[1] Proper understanding of drug substance properties is essential for pharmaceutical development to maintain the critical quality attributes throughout the product shelf life. A detailed understanding of the properties of the drug substance helps to minimize formulation problems in later stages of drug development and reduce drug development costs.

An important part of developing any dosage form is a proper understanding of drug substance properties and excipient selection. It is preferable to use excipients that are compatible with the drug substance to maximize drug-product stability and to have desired bioavailability. It is critical to understand the physicochemical properties of the drug substance, and pre-formulation compatibility studies will help identify incompatibilities so that certain excipients can be avoided during the pharmaceutical development of drug product for better drug product stability.

Atorvastatin calcium is a synthetic lipid-lowering agent.[2] Atorvastatin 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. Atorvastatin calcium tablets are indicated as an adjunct therapy to diet to:[2]

- Reduce the risk of MI, stroke, revascularization procedures, and angina in patients without CHD, but with multiple risk factors.
- Reduce the risk of MI and stroke in patients with type 2 diabetes without CHD, but with multiple risk factors.
- Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF, and angina in patients with CHD.
- Reduce elevated total-C, LDL-C, apo B, and TG levels and increase HDL-C in adult patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia.
- Reduce elevated TG in patients with hypertriglyceridemia and primary dysbetalipoproteinemia.
- Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH).
- Reduce elevated total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy.

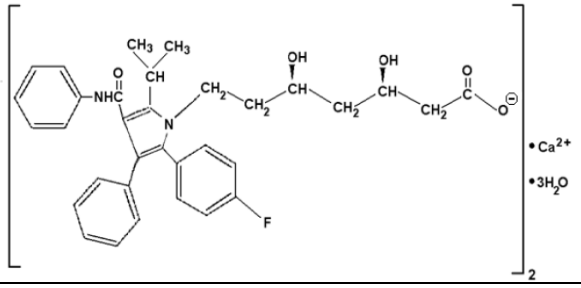
Atorvastatin Calcium Tablets have been approved in 10, 20, 40, or 80 mg of Atorvastatin strengths for oral route of administration.

EXPERIMENTAL

Physicochemical Properties of Atorvastatin Calcium

Please refer to Table 1 for the physicochemical properties of Atorvastatin Calcium.

Table 1: Physicochemical Properties of Atorvastatin Calcium.

Chemical Name	[R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1Hpyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate
Chemical Structure[3]	
Formula[3]	(C33H34 FN2O5)2Ca•3H2O
Molecular weight[3]	1209.42
Appearance	A white to off-white crystalline powder
Melting Range	Between 159.2°C and 160.7°C
pKa	11.82
pH:	Atorvastatin Calcium providing a pH equal to or greater than the pKa 1 of Atorvastatin Calcium to an aqueous solution thereof.
Specific Optimal Rotation	Between (-) 6.0° and (-) 10.0° (In 1% DMSO solution)
Polymorphism	Atorvastatin Calcium exhibits amorphous nature.
Stereochemistry	There are two chiral centers in Atorvastatin Calcium. This affords two geometrical isomeric pairs and four stereo isomers. Atorvastatin is a single enantiomeric pair having R, R configuration at both the hydroxyl groups.
Hygroscopicity	Atorvastatin Calcium is highly Hygroscopic

The aqueous solubility as a function of pH at 37°C

Medium	Final pH	Solubility (mg/mL)	Solubility (mg/250ml)	Remarks
pH 4.5 Acetate buffer	4.50	0.0817	979.19	Low Soluble
Purified Water	5.85	0.2803	285.41	Low Soluble
pH 6.8 phosphate buffer	6.80	0.3017	265.16	Low Soluble
pH 7.5 phosphate buffer	7.50	0.3071	260.50	Low Soluble

Since the dose solubility is greater than 250 mL, based on BCS Classification, the drug substance (Atorvastatin Calcium) is low soluble in Purified Water, pH 4.5 Acetate buffer, pH 6.8 Phosphate buffer, and pH 7.5 Phosphate buffer. As Atorvastatin Calcium tends to degrade in 0.1 N HCl (pH 1.2), solubility data is not established in this Medium.

Compatibility of Atorvastatin Calcium with Inactive Ingredients

Excipients compatibility studies were carried out to study the compatibility of various excipients with Atorvastatin Calcium. Each excipient was individually mixed with Atorvastatin Calcium (API) and this blend was kept in a closed transparent glass vial at 40°C/75% RH for four weeks. The samples were analyzed for Related Compounds to determine the drug excipient's compatibility. The initial and 4 weeks results of excipients compatibility are presented in Table 2 and Table 3 respectively.

RESULTS AND DUSCUSSION

Table 2. Excipients Compatibility with Atorvastatin Calcium (Initial Data).

Excipients with Atorvastatin Calcium	Drug: Excipient Ratio	Impurity A	Impurity B	Impurity D	3-O-methyl	Lactone	Dio methyl ester	Highest Unknown	Total Impurity
Atorvastatin Calcium	-	0.091	0.053	0.122	0.029	0.107	0.058	0.042	0.560
Atorvastatin Calcium: Microcrystalline Cellulose (Flocel 102),NF	1:1	0.090	0.053	0.112	0.036	0.105	0.046	0.033	0.520
Atorvastatin Calcium: Lactose Monohydrate (Flowlac 100), NF	1:1	0.076	0.044	0.091	0.029	0.089	0.043	0.030	0.410
Atorvastatin Calcium: Hypromellose 6 cps, NF	1:0.1	0.094	0.054	0.120	0.033	0.108	0.053	0.036	0.525
Atorvastatin Calcium : Hydroxypropyl cellulose (Klucel LF), NF	1:0.1	0.091	0.055	0.141	0.032	0.106	0.054	0.048	0.553
Atorvastatin Calcium: Sodium Carbonate anhydrous, NF	1:0.1	0.087	0.049	0.118	0.037	0.087	0.044	0.037	0.465
Atorvastatin Calcium: Meglumine, NF	1:0.1	0.092	0.053	0.106	0.039	0.087	0.044	0.047	0.475
Atorvastatin Calcium: Croscarmellose Sodium (Disolcel), NF	1:0.1	0.093	0.055	0.128	0.038	0.110	0.056	0.053	0.535
Atorvastatin Calcium: ,Magnesium Stearate, NF	1:0.01	0.088	0.053	0.122	0.030	0.100	0.046	0.045	0.525
Atorvastatin Calcium: Opadry II white 85F18422, NF	1:0.1	0.085	0.050	0.120	0.036	0.104	0.053	0.045	0.539
Atorvastatin Calcium: Polysorbate 80 NF	1:0.01	0.077	0.044	0.127	0.033	0.107	0.048	0.043	0.522

Table 3. Excipients Compatibility with Atorvastatin Calcium (4 weeks Data).

Excipients with Atorvastatin Calcium	Drug: Excipient Ratio	4 Weeks @ 40^{0}C/75% RH in Closed glass vial							
		Impurity A	Impurity B	Impurity D	3-O-methyl	Lactone	Dio methyl ester	Highest Unknown	Total Impurity
Atorvastatin Calcium	-	0.087	0.049	0.128	0.056	0.112	ND	0.045	0.525
Atorvastatin Calcium : Microcrystalline Cellulose (Flocel 102),NF	1:1	0.074	0.047	0.115	0.049	0.102	ND	0.036	0.460
Atorvastatin Calcium : Lactose Monohydrate (Flowlac 100), NF	1:1	0.071	0.053	0.102	0.058	0.086	ND	0.032	0.470
Atorvastatin Calcium : Hypromellose 6 cps, NF	1:0.1	0.076	0.047	0.128	0.040	0.112	ND	0.036	0.480
Atorvastatin Calcium : Hydroxypropyl cellulose (Klucel LF), NF	1:0.1	0.076	0.051	0.140	0.040	0.109	ND	0.050	0.550
Atorvastatin Calcium : Sodium Carbonate anhydrous, NF	1:0.1	0.087	0.049	0.117	0.046	0.093	ND	0.040	0.458
Atorvastatin Calcium : Meglumine, NF	1:0.1	0.085	0.048	0.122	0.044	0.076	ND	0.045	0.510
Atorvastatin Calcium : Croscarmellose Sodium (Disolcel), NF	1:0.1	0.095	0.051	0.125	0.053	0.115	ND	0.052	0. 550
Atorvastatin Calcium : ,Magnesium Stearate, NF	1:0.01	0.091	0.050	0.118	0.050	0.102	ND	0.046	0.487
Atorvastatin Calcium : Opadry II white 85F18422, NF	1:0.1	0.083	0.046	0.122	0.048	0.108	ND	0.048	0.535
Atorvastatin Calcium : Polysorbate 80 NF	1:0.01	0.040	0.026	0.125	0.038	0.120	ND	0.043	0.480

Impurity A: Desfluoro impurity
Impurity B: 3*S*,5*R* Isomer.
Impurity D: Epoxide impurity.

CONCLUSION

Data indicated that the impurity profile of the blend of Atorvastatin Calcium and Excipients were found to be unchanged even after four weeks at 40°C/ 75% RH. It was, therefore, concluded from the above experiment that the tested excipients are compatible with Atorvastatin Calcium and were acceptable for use in the Atorvastatin Calcium Tablets.

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