INFLUENCE OF OMEPRAZOL AND RAMIPRIL ON *IN-VITRO* DISSOLUTION OF ATORVASTATIN10mg TABLET WITH

TO DETERMINE THE DRUG-DRUG INTERACTION

Submitted by:

Fahmia Rashid

ID NO.: 2010-1-70-022

Department of Pharmacy

East West University

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A thesis report, submitted to the Department of Pharmacy, East West University, in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy.

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CERTIFICATE BY THE CHAIRPERSON

This is to certify that the dissertation entitled "Influence of Omprazol and Ramipril on *In-Vitro* Dissolution of Atorvastatin 10mg Tablet to Determine the Drug-Drug Interaction"**,** is a bonafide research work done by **Fahmia Rashid,** ID: 2010-1-70-022 in partial fulfillment of the requirement for the Degree of Bachelor of Pharmacy.

_____

Dr. Chowdhury Faiz Hossain

Chairperson & Professor

Department of Pharmacy

East West University

Aftabnagar,Dhaka

CERTIFICATE

This is to certify that, the research work on "Influence of Omprazol and Ramipril on *In-Vitro* Dissolution of Atorvastatin 10mg Tablet to Determine the Drug-Drug Interaction" submitted to the Department of Pharmacy, East West University, Dhaka, Bangladesh, in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (B.Pharm) was carried out by **Fahmia Rashid**, ID: 2010-1-70-022, under our guidance and supervision and that no part of the thesis has been submitted for any other degree. We further certify that all the resources of the information in this connection are duly acknowledged.

Nigar Sultana Tithi
Lecturer and Research Supervisor
Department of Pharmacy
East West University
Aftabnagar, Dhaka.

Mehreen Rahman
Lecturer and Research Co-supervisor
Department of Pharmacy
East West University
Aftabnagar, Dhaka.

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Dedicated

To

My Loving Parents

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Abstract

The main objective of this study was to determine the change of pharmacokinetic property; specially dissolution of Atorvastatin when it's taken with combination of two drugs; Ramipril and Omeprazol. Atorvastatin is a widely used lipid lowering drug which is usually prescribed with various drugs like Omeprazol, Ramipril, Metformin, Multivitamin etc usually after dinner, what came out in some recent prescriptions collected before the study. Famous brand of these drugs were used, as in Lipicon 10mg for Atorvastatin, Ramoril 2.5mg for Ramipril, Cosec 20mg for Omeprazol so that a standard value of percent dissolution can be achieved. First the dissolution profile of Atorvastatin individually was studied going through the standard *in-vitro* dissolution test then the same procedure was run using Atorvastatin, Ramipril and Omeprazol in combination. However, it was found out from the study that Atorvastatin showed a greater percent of dissolution when taken with combination of those drugs than that of only Atorvastatin. From time range of 5min to 30min dissolution rate of Atorvastatin increased gradually. After 5min, 10min, 15min and 30min dissolution rate of atorvastatin was 2.093%,2.64%,7.01 %,36.14% respectively, and for the combination these were 5.063%,11.872%,32.38%,63.641% respectively. It means that if patients take Atorvastatin along with Ramipril and Omeprazol at a time, dissolution rate of Atorvastatin increases.

Chapter One: Introduction

1.1 Atorvastatin:

The statins inhibit the enzyme HMG-CoA reductase, the rate-limiting enzyme of the mevalonate pathway of cholesterol synthesis, thus lowering blood cholesterol levels. Statins also have additional cardiovascular benefits that appear to be independent of their effects on cholesterol synthesis. Atorvastatin is an HMG-CoA reductase inhibitor (IC_{50} = 154 nM) that is effective in treating hypercholesterolemia and certain dyslipidemias. It may also be used to prevent coronary or stroke events in hypertensive patients with normal cholesterol levels. In addition to inhibiting cholesterol synthesis, atorvastatin reduces the production of low-density lipoprotein (LDL). It is metabolized by cytochrome P450 3A4 (CYP3A4), producing several metabolites that are important in the therapeutic actions attributed to atorvastatin. As a result, inhibitors or inducers of CYP3A4 modify plasma concentrations of atorvastatin and its metabolites, altering the effectiveness of treatment. (World health Organization, 2013)

Synonyms	• Cardyl • Lipitor®
Formal Name	2-(4-fluorophenyl)-βR,δR-dihydroxy-5- (1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1- heptanoic acid}]
CAS Number	134523-00-5
Molecular Formula	$C_{33}H_{35}FN_2O_5$
Formula Weight	558.6
Formulation	A crystalline solid
Purity	≥98%
Stability	2 years
Storage	-20°C

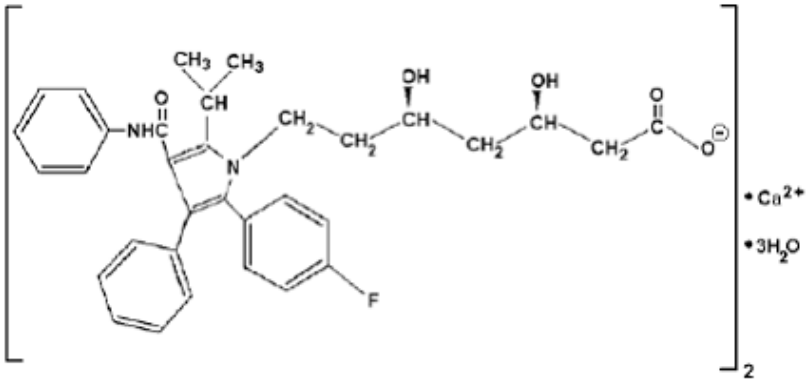


Fig1: Structure of Atorvastatin (Naoumova, Dunn, 1997)

1.2 History:

The cholesterol lowering medications known as “statins” have been around since the 1980’s. Statins work by blocking our body from the body from making cholesterol. Although our bodies need some cholesterol to function properly, high levels of cholesterol can cause cardio-vascular disease that in turn can lead to heart attacks and strokes. When the first statin drug was approved for sale in 1987 the United States by the U.S. Food & Drug Administration (FDA), the medication was only approved for use with people who had high levels of cholesterol in their blood and who had not been able to lower cholesterol levels with dietary changes and exercise. Due in part to influence from drug companies seeking to expand the market for statin drugs, the FDA later approved the use of statin drugs for the prevention of cardio-vascular disease. This expanded market cause profits to soar at drug companies selling statin drugs.

Atorvastatin was approved by the FDA in late 1996. It was created by the drug company Warner-Lambert, who also made after the counter products such as Listerine and Benadryl. Warner-Lambert partnered with Pfizer, another large drug company, to market and sell Atorvastatin. Pfizer used a well trained sales force to call on doctors and to sell them on writing prescriptions for Atorvastatin. Pfizer also started a direct to consumer marketing campaign for Liptor using TV ads and magazine ads. Pfizer saw the huge profit margins in Atorvastatin and Pfizer eventually bought out Warner-Lambert in 2000. Atorvastatin went on to become the top-selling drug in the history of prescription medications. More than 17 million people have taken Atorvastatin and Atorvastatin sales to date have exceeded $120 billion dollars. Even though generic Atorvastatin became available to the public in late 2011, many people still buy name brand Atorvastatin and Pfizer still makes over $2 billion dollars a year selling name brand Atorvastatin.(Dan Chapman & Associates, *LLC*,2013)

1.3 Chemistry:

1.3.1 Synthesis:

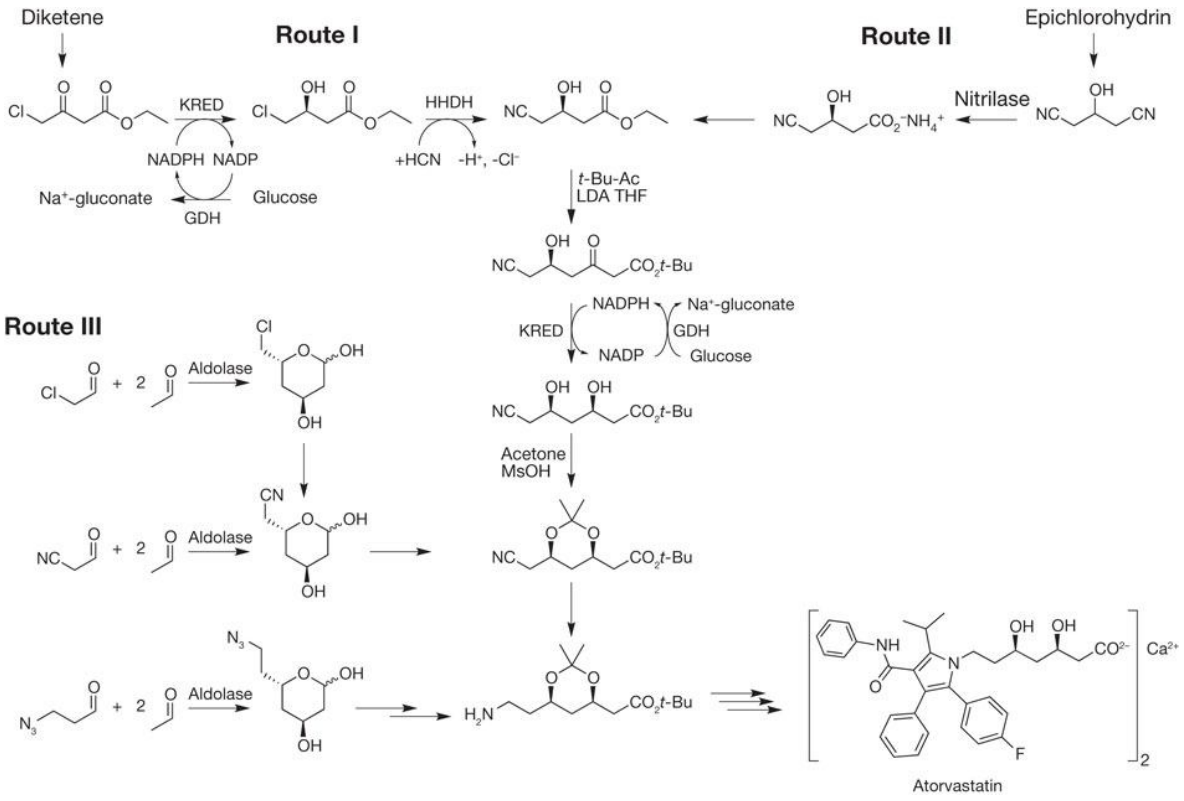


Fig2: Synthesis of Atorvastatin

These processes use the combination of KRED with a halohydrin dehalogenase (HHDH) (route I), a nitrilase (route II) or an aldolase (route III). They differ not only in class of enzyme, but also in choice of (inexpensive) starting material, activity and selectivity of the biocatalyst, downstream processing, and yield and purity of final product. Routes I and II create one stereocentre, but route III creates both stereocentres required for the advanced pharmaceutical intermediate. Introduction of the second chiral centre following routes I and II is also accomplished using KRED. LDA, lithium diisopropylamide; t-Bu, tert-butyl; THF, tetrahydrofuran. (Molecular Chemistry – Medicinal Chemistry,Université de Rennes 1 – Vietnam National University,Hanoi ,2011-2012)

1.3.2 Chemical nature:

Volume of distribution: 381 L

Protein Binding: >98% bound to plasma proteins

Half Life: 14 hours, but half-life of HMG-CoA inhibitor activity is 20-30 hours due to longer-lived active metabolites. (Rouleau, 2005 Dec., Maggon 2005 Jun 1)

1.3.3 Physicochemical Properties:

State	Solid	
Experimental Properties	Property	Value
	melting point	159.2-160.7 °C
	water solubility	Sodium salt soluble in water, 20.4 ug/mL (pH 2.1), 1.23 mg/mL (pH 6.0)
	logP	5.7
Predicted Properties	water solubility	6.30e-04 g/l
	logP	4.24
	logS	-6
	pKa (strongest acidic)	4.33
	pKa (strongest basic)	-2.7
	physiological charge	-1
	hydrogen acceptor count	5
	hydrogen donor count	4
	polar surface area	111.79
	rotatable bond count	12
	refractivity	158.2
	polarizability	59.25

Table1: Physicochemical Properties of Atorvastatin (Rouleau, 2005 Dec., Maggon 2005 Jun 1)

1.4 Mechanism of action/ Pharmacodynamics:

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3- methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels

of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

In animal models, Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell surface to enhance uptake and catabolism of LDL; Atorvastatin also reduces LDL production and the number of LDL particles. Atorvastatin reduces LDL-C in some patients with homozygous familial hypercholesterolemia (FH), a population that rarely responds to other lipid-lowering medication(s). (U.S. Food and Drug Administration, 2013)

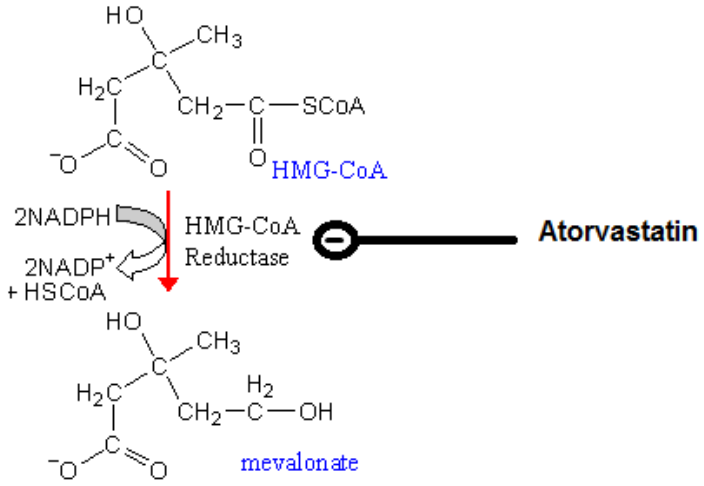


Fig3: Mechanism of action of atorvastatin

1.5 Pharmacokinetics:

1.5.1 Absorption:

Atorvastatin is rapidly absorbed after oral administration with maximum plasma concentrations achieved in 1 to 2 hours. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic bioavailability is due to presystemic clearance by gastrointestinal mucosa and first-pass metabolism in the liver. (U.S. FDA, 2013)

1.5.2 Distribution:

Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is 98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be secreted in human milk. (U.S. FDA, 2013)

1.5.3 Metabolism:

Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. In vitro inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. In vitro studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this isozyme. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation. (U.S. FDA, 2013)

1.5.4 Excretion:

Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration. (U.S.FDA, 2013)

1.6 Therapeutic Use:

1.6.1 Prevention of Cardiovascular Disease

In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, atorvastatin is indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke
- Reduce the risk for revascularization procedures and angina

In patients with type 2diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, atorvastatin is indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke

In patients with clinically evident coronary heart disease, atorvastatinis indicated to:

- Reduce the risk of non-fatal myocardial infarction
- Reduce the risk of fatal and non-fatal stroke
- Reduce the risk for revascularization procedures
- Reduce the risk of hospitalization for CHF
- Reduce the risk of angina. (Chelmow, Dunn& John, 2013)

1.6.2 Hyperlipidemia

Atorvastatin is indicated:

- As an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb);
- As an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV);
- For the treatment of patients with primary dysbetalipoproteinemia (Fredrickson Type III) who do not respond adequately to diet;
- To reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipidlowering treatments (e.g., LDL aphaeresis) or if such treatments are unavailable;
- As an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:
  a. LDL-C remains ≥ 190 mg/dL or
  b. LDL-C remains ≥ 160 mg/dL and:

There is a positive family history of premature cardiovascular disease or two or more other CVD risk factors are present in the pediatric patient. (Chelmow, Dunn& John, 2013)

1.7 Dose and Dosage form:

1.7.1 Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb):

The recommended starting dose of atorvastatin is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of atorvastatin is 10 to 80 mg once daily. Atorvastatin can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of atorvastatin should be individualized according to patient characteristics such as goal

of therapy and response. After initiation and/or upon titration of atorvastatin, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

1.7.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age):

The recommended starting dose of atorvastatin is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy. Adjustments should be made at intervals of 4 weeks or more.

1.7.3 Homozygous Familial Hypercholesterolemia:

The dosage of atorvastatin in patients with homozygous FH is 10 to 80 mg daily. LIPITOR should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable. (Chelmow, Dunn& John, 2013)

1.8 Side Effects:

More common

- Headache
- hoarseness
- lower back or side pain
- pain or tenderness around the eyes and cheekbones
- painful or difficult urination
- stuffy or runny nose

Less common

- Abdominal or stomach pain
- back pain
- belching or excessive gas
- constipation
- general feeling of discomfort or illness
- heartburn, indigestion, or stomach discomfort
- lack or loss of strength
- loss of appetite
- nausea
- shivering
- sweating
- trouble sleeping & vomiting (Chelmow, Dunn& John, 2013)

1.9 Adverse Effects:

1. Rhabdomyolysis and myopathy

2. Liver enzyme abnormalities. (Chelmow, Dunn& John, 2013)

1.10 Drug-Drug Interaction:

1.10.1 Severe Interactions of Atorvastatin oral:

These medications are not usually taken together. Patient should consult their healthcare professional (e.g., doctor or pharmacist) for more information:

This information is generalized and not intended as specific medical advice. Consult your healthcare professional before taking or discontinuing any drug or commencing any course of treatment.

	How the interaction occurs:	**What might happen**	**Reference**
Selected HMG-CoA Reductase Inhibitors/ Telithromycin:	Telithromycin may slow down metabolism of cholesterol medicine in liver	The blood levels of cholesterol medicine may increase	Sanofi-Aventis June 2, 2009., Merck & Co., Inc. February, 2012.USFood and Drug Administration. June 8, 2011.
Atorvastatin (> 40 mg); Lovastatin; Simvastatin/Boceprevir	Boceprevir may slow down metabolism of cholesterol medicine in liver	The amount of cholesterol medicine in blood may increase	Schering Corporation, February, 2013. Merck & Co., Inc. February, 2012., Pfizer Inc. October, 2012.
Atorvastatin (>20mg)/Darunavir; Fosamprenavir; Saquinavir	Protease inhibitors may slow down metabolism of atorvastatin in liver	The amount of atorvastatin in blood may increase	Pfizer Inc. October, 2012.,Tibotec Inc. February, 2013.,GlaxoSmithKline February, 2013

Atorvastatin (> 40mg)/Nelfinavir	Nelfinavir may slow down how quickly your liver processes atorvastatin.	The amount of atorvastatin in blood may increase	Pfizer Inc. October, 2012. Agouron Pharmaceutic als, Inc. May, 2013. Hsyu , Schultz-Smith, Lillibridge , Lewis , Kerr,2001 Dec
Mibefradil /Selected Agents	Body may not process cholesterol medicines properly	Blood levels of cholesterol medicine may increase and cause muscle pain or flu-like symptoms	Roche Pharmaceutic als, December 1997
Selected Azoles/Selected HMG-CoA Reductase Inhibitors	Body may not process cholesterol medicines properly	Blood levels of cholesterol medicine may increase	Merck & Co., Inc. February, 2012.

Table2: Severe Interactions of Atorvastatin oral

1.10.2 Serious Interactions of Atorvastatin oral:

These medications may interact and cause very harmful effects. Consult your healthcare professional (e.g., doctor or pharmacist) for more information. This information is generalized and not intended as specific medical advice. Consult your healthcare professional before taking or discontinuing any drug or commencing any course of treatment.

	How the interaction occurs	**What might happen**	**Reference**
Selected HMG-CoA Reductase Inhibitors/ Gemfibrozil	Not known	Severe muscle pain, flu-like symptoms, and sudden decrease in the amount of urine.	Thompson,Ford,Jenkinson,Trayner, 1986 Aug

Atorvastatin;Lovastatin/ Cyclosporine	Not known	Muscle aches, tenderness, or weakness.	Pfizer Inc. October, 2012.
HMG-CoA Reducates Inhibitors/Niacin (=> 250 mg)	Not known. This interaction may be more likely to occur in patients of Chinese descent.	Muscle aches, tenderness, and weakness.	Merck & Co., Inc. February, 2012
Atorvastatin; Cerivastatin/Nefazodone	Nefazodone may slow down body's ability to process cholesterol medicine.	The levels of the cholesterol medicine may increase in blood. This may cause damage to muscles.	Bristol-Myers Squibb Company ,January, 2005.
HMG-CoA Reductase Inhibitors/Selected Fibrates	Not known	Muscle pain, flu-like symptoms, and sudden decrease in the amount of urine	Goldman , Fishman , Lee, Johnson,1989 Mar

Table3: Serious Interactions of Atorvastatin oral

1.10.3 Moderate Interactions of Atorvastatin oral:

These medications may cause some risk when taken together. Consult your healthcare professional (e.g., doctor or pharmacist) for more information.

	How the interaction occurs	**What might happen**	**Reference**
Selected HMG-CoA Reductase Inhibitors/Rifampin	Rifampin may increase how quickly your intestines and liver process your cholesterol	The amount of cholesterol medicine in your blood may decrease. It may not work as well and your cholesterol levels may not decrease as much	Kyrklund , Backman , Kivisto , Neuvonen , Laitila , Neuvonen,

	medicine.		2000 Dec
Atorvastatin; Lovastatin (<=40mg); Simvastatin (<=20mg)/Amiodarone	Amiodarone may slow down how quickly your liver processes your cholesterol medicine.	The amount of cholesterol medicine in your blood may increase. This could increase your risk for muscle soreness or damage.	Wyeth Pharmaceuticals,November, 2011.
Atorvastatin/Selected Protease Inhibitors	Protease inhibitors may slow down how quickly your liver processes atorvastatin.	The amount of atorvastatin in your blood may increase and cause harmful effects.	GlaxoSmithKline May, 2005
Selected HMG Co-A Reductase Inhibitors/Efavirenz	Efavirenz may speed up how quickly your liver processes your cholesterol medicine	The amount of cholesterol medicine in your blood may decrease and it may not work as well	Gerber , Rosenkranz , Fichtenbaum , 2005 Jul
Selected HMG-CoA Reductase Inhibitors/Bosentan	Bosentan may speed up how quickly your liver processes your cholesterol medicine.	The amount of cholesterol medicine in your blood may decrease and it may not work as well.	Dingemanse, Schaarschmidt , Giersbergen ,2003
HMG-CoA Reductase Inhibitors/ Digoxin	Not known	Increase the amount of cholesterol medicine in blood, which can cause muscle problems. Some cholesterol medicines (atorvastatin and simvastatin) may increase the amount of digoxin in blood and cause side effects.	(Bellosta, Paoletti , Corsini , 2004 Jun 15

Table4: Moderate Interactions of Atorvastatin oral

1.11 Contraindications:

Active liver disease or unexplained persistent elevations of serum transaminases Hypersensitivity to any component of this medication. Pregnancy and lactation: Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. (Remedy Health Media, LLC, 2014)

1.12 Drug interactions overview:

Whenever two or more drugs are being taken, there is a chance that there will be an interaction among the drugs. The interaction may increase or decrease the effectiveness of the drugs or the side effects of the drugs. The likelihood of drug interactions increases as the number of drugs being taken increases. Therefore, people who take several drugs are at the greatest risk for interactions. Drug interactions contribute to the cost of healthcare because of the costs of medical care that are required to treat problems caused by changes in effectiveness or side effects. Interactions also can lead to psychological suffering that can be avoided. This review discusses the issue of drug interactions and several ways to avoid them.

A drug interaction can be defined as an interaction between a drug and another substance that prevents the drug from performing as expected. This definition applies to interactions of drugs with other drugs (drug-drug interactions), as well as drugs with food (drug-food interactions) and other substances.

1.12.1 How drug interactions occurs:

There are several mechanisms by which drugs interact with other drugs, food, and other substances. An interaction can result when there is an increase or decrease in:

1. the absorption of a drug into the body;
2. distribution of the drug within the body;
3. alterations made to the drug by the body (metabolism); and
4. elimination of the drug from the body.

Most of the important drug interactions result from a change in the absorption, metabolism, or elimination of a drug. Drug interactions also may occur when two drugs that have similar (additive) effects or opposite (canceling) effects on the body are administered together. For example, there may be major sedation when two drugs those have sedation as side effects are

given, for example, narcotics and antihistamines. Another source of drug interactions occurs when one drug alters the concentration of a substance that is normally present in the body. The alteration of this substance reduces or enhances the effect of another drug that is being taken. The drug interaction between warfarin (Coumadin) and vitamin K-containing products is a good example of this type of interaction. Warfarin acts by reducing the concentration of the active form of vitamin K in the body. Therefore, when vitamin K is taken, it reduces the effect of warfarin.

1.12.2 Change in absorption by drug interaction

Most drugs are absorbed into the blood and then travel to their site of action. Most drug interactions that are due to altered absorption occur in the intestine. There are various potential mechanisms through which the absorption of drugs can be reduced. These mechanisms include:

1. an alteration in blood flow to the intestine;
2. change in drug metabolism (breakdown) by the intestine;
3. increased or decreased intestinal motility (movement);
4. alterations in stomach acidity, and
5. a change in the bacteria that reside in the intestine.

Drug absorption also can be affected if the drug's ability to dissolve (solubility) is changed by another drug or if a substance (for example, food) binds to the drug and prevents its absorption.

Change in drug metabolism and elimination by drug interaction

Most drugs are eliminated through the kidney in either an unchanged form or as a by-product that results from the alteration (metabolism) of the drug by the liver. Therefore, the kidney and the liver are very important sites of potential drug interactions. Some drugs are able to reduce or increase the metabolism of other drugs by the liver or their elimination by the kidney.

Metabolism of drugs is the process through which the body converts (alters or modifies) drugs into forms that are more or less active (for example, by converting drugs that are given in inactive forms into their active forms that actually produce the desired effect) or that are easier for the body to eliminate through the kidneys. Most drug metabolism takes place in the liver, but other organs also may play a role (for example, the kidneys, intestine, etc.). The cytochrome P450 enzymes are a group of enzymes in the liver that are responsible for the metabolism of most drugs. They are, therefore, often involved in drug interactions. Drugs and certain types of food may increase or decrease the activity of these enzymes and therefore affect the concentration of drugs that are metabolized by these enzymes. An increase in the activity of these enzymes leads to a decrease in the concentration and effect of an

administered drug. Conversely, a decrease in enzyme activity leads to an increase in drug concentration and effect.

1.12.3 The consequences of drug interactions:

Drug interactions may lead to an increase or decrease in the beneficial or the adverse effects of the given drugs. When a drug interaction increases the benefit of the administered drugs without increasing side effects, both drugs may be combined to increase the control of the condition that is being treated. For example, drugs that reduce blood pressure by different mechanisms may be combined because the blood pressure lowering effect achieved by both drugs may be better than with either drug alone.

The absorption of some drugs is increased by food. Therefore, these drugs are taken with food in order to increase their concentration in the body and, ultimately, their effect. Conversely, when a drug's absorption is reduced by food, the drug is taken on an empty stomach.

Drug interactions that are of greatest concern are those that reduce the desired effects or increase the adverse effects of the drugs. Drugs that reduce the absorption or increase the metabolism or elimination of other drugs tend to reduce the effects of the other drugs. This may lead to failure of therapy or warrant an increase in the dose of the affected drug. Conversely, drugs that increase absorption or reduce the elimination or metabolism of other drugs - increase the concentration of the other drugs in the body - and lead to increased amounts of drug in the body and more side effects. Sometimes, drugs interact because they produce similar side effects. Thus, when two drugs that produce similar side effects are combined, the frequency and severity of the side effect are increased.

1.12.4 The frequency of drug interactions:

The prescribing information for most drugs contains a list of potential drug interactions. Many of the listed interactions may be rare, minor, or only occur under specific conditions and may not be important. Drug interactions that cause important changes in the action of a drug are of greatest concern.

Drug interactions are complex and chiefly unpredictable. A known interaction may not occur in every individual. This can be explained because there are several factors that affect the likelihood that a known interaction will occur. These factors include differences among individuals in their:

- genes,
- physiology,

- age,
- lifestyle (diet, exercise),
- underlying diseases,
- drug doses,
- the duration of combined therapy, and
- the relative time of administration of the two substances. (Sometimes, interactions can be avoided if two drugs are taken at different times.)

Nevertheless, important drug interactions occur frequently and they add millions of dollars to the cost of health care. Moreover, many drugs have been withdrawn from the market because of their potential to interact with other drugs and cause serious health care problems. (Ogbru, 2013)

Chapter two: Dissolution Test

2.1 Quality parameter test:

Quality parameter tests are performed as per the pharmacopoeial standards. These tests are measure of the quality of the various dosage form of drug. Each of the pharmacopoeia like the USP, BP, IP etc each have their own set of standards and specify disintegration tests of their own. USP, European pharmacopoeia and Japanese pharmacopoeia have been harmonized by the International conference on Harmonization (ICH) and are interchangeable. The quality parameter tests are: (British Pharmacopoeia, 2012 Online)

2.1.1 Disintegration test:

The disintegration test is performed to find out the time it takes for a solid oral dosage form like a tablet or capsule to completely disintegrate. The time of disintegration is a measure of the quality. This is because, for example, if the disintegration time is too high; it means that the tablet is too highly compressed or the capsule shell gelatin is not of pharmacopoeial quality or it may imply several other reasons. And also if the disintegration time is not uniform in a set of samples being analyzed, it indicates batch inconsistency and lack of batch uniformity. (BP, 2012 Online)

2.1.2 Dissolution Test:

Dissolution is the process by which a solid solute enters a solution. In the pharmaceutical industry, it may be defined as the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition. Dissolution is considered one of the most important quality control tests performed on pharmaceutical dosage forms and is now developing into a tool for predicting bioavailability, and in some cases, replacing clinical studies to determine bioequivalence. Dissolution behavior of drugs has a significant effect on their pharmacological activity. In fact, a direct relationship between in vitro dissolution rate of many drugs and their bioavailability has been demonstrated and is generally referred to as in vitro-in vivo correlation, IVIVC. (BP, 2012 Online)

2.1.3 Weight Variation test:

Tablet weight is mainly affected by factors such as tooling of the compression machine, head pressure, machine speed and flow properties of the powder. Inconsistent powder or granulate

density and particle size distribution are common sources of weight variation during compression.Variation between tablet with respect to dose and weight must be reduced to a minimum. Uniformity of weight is an in process test parameter which ensures consistency of dosage units during compression.

IP/BP & USP limits for tablet weight variation is given below: (BP, 2012 Online)

IP/BP	Limit	USP
80 mg or less	± 10%	130mg or less
More than 80mg or Less than 250mg	± 7.5%	130mg to 324mg
250mg or more	± 5%	More than 324mg

Table5: Standard for weight variation

2.1.4 Hardness test:

In this test method, the tablet is placed between two platens (jaws), one of which is attached to a load cell and the other to a motor which provides the mechanical drive. During testing, the motorized jaw drives forward pressing the tablet against the fixed jaw until such time as the tablet breaks whereupon the motorized jaw retracts and the load required to break the tablet is recorded. (BP, 2012 Online)

2.1.5 Friability test:

Friability is the tendency for a tablet to chip, crumble or break following compression. This tendency is normally confined to uncoated tablets and surfaces during handling or subsequent storage.

The basic Friability Tester comprises of a drum and a motor capable of rotating the drum at 25 rpm. The standard friability drum has an inside diameter of 287 mm and a depth of 38 mm and is fitted with a curved baffle which subjects the tablets to be tested to a drop of 156 mm. (BP, 2012 Online)

2.1.6 Content Uniformity Test:

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch. Due to increased awareness of physiological availability, the content uniformity test has been included in the monographs of all coated and uncoated tablets and all capsules intended for oral administration where the range of size of the dosage form available include 50mg or smaller sizes. Tablet monographs with a content uniformity requirement do not have weight variation requirements. For content uniformity test, representative samples of 30tablets are selected

and 10 are assayed individually. At least 9must assay within ±15% of the declared potency and none may exceed ±25% [3.]

$$s = \left[\frac{\Sigma(x_i - \overline{X})^2}{n-1}\right]^{1/2}$$

$$RSD = \frac{100s}{\overline{X}}.$$

Equation1: Content uniformity test

s = Sample standard deviation

RSD= Relative standard deviation (the sample standard deviation expressed as a percentage of the mean)

Bar (X)= Mean of the values obtained from the units test, expressed as the percentage of the label claim

n= Number of the units tested

$x_1, x_2, x_3 \ldots\ldots x_n$= Individual values ($x_i$) of the units tested , expressed as the percentage of label claim . (BP, 2012 Online)

2.2.1 Importance of dissolution study:

1. Results from in-vitro dissolution rate experiments can be used to explain the observed differences in *in-vivo* availability.

2. Dissolution testing provides the means to evaluate critical parameters such as adequate bioavailability and provides information necessary to formulator in development of more efficacious and therapeutically optimal dosage forms.

3. Most sensitive and reliable predictors of in-vivo availability.

4. Dissolution analysis of pharmaceutical dosage forms has emerged as single most important test that will ensure quality of product.

5. It can ensure bioavailability of product between batches that meet dissolution criteria.

6. Ensure batch-to-batch quality equivalence both in-vitro and in-vivo, but also to screen formulations during product development to arrive at optimally effective products.
7. Physicochemical properties of model can be understood needed to mimic in-vivo environment.

8. Such models can be used to screen potential drug and their associated formulations for dissolution and absorption characteristics.

9. Serve as quality control procedures, once the form of drug and its formulation have been finalized. (Sing, Jan 15, 2012)

2.2.2 Application of dissolution study:

1. Product development
Important tool during development of dosage form. Aids in guiding the selection of prototype formulations and for determining optimum levels of ingredients to achieve drug release profiles, particularly for extended release formulations.
Also guides in selection of a "market-image" product to be used in pivotal in-vivo bioavailability or bioequivalence studies. (Sing, Jan 15, 2012)

2. Quality assurance
D.T. performed on future production lots and is used to assess the lot-to-lot performance characteristics of drug product and provide continued assurance of product integrity/similarity. (Sing, Jan 15, 2012)

3. Product stability
In-vitro dissolution also used to assess drug product quality with respect to stability and shelf-life. As product age, physicochemical changes to the dosage form may alter dissolution characteristics of drug product over time. For some products, polymorph transformations to more stable, and hence less soluble crystalline forms may result in reduced dissolution rates. (Sing, Jan 15, 2012)

4. Comparability assessment
Also useful for assessing the impact of pre-or post-approval changes to drug product such as changes to formulation or manufacturing process. Thus, in-vitro comparability assessment is critical to ensure continued performance equivalency and product similarity. (Sing, Jan 15, 2012)

5. Waivers of in-vivo bioequivalence requirements
In-vitro dissolution testing or drug release testing may be used for seeking waiver of required product to conduct in-vivo bioavailability or bioequivalence studies. (Sing, Jan 15, 2012)

2.3 Factors affecting dissolution rate:

1. Physicochemical Properties of Drug

2. Drug Product Formulation Factors

3. Processing Factors

4. Factors Relating Dissolution Apparatus

5. Factors Relating Dissolution Test Parameters

2.3.1 Physicochemical properties of drug:

a) Drug solubility

Solubility of drug plays a prime role in controlling its dissolution from dosage form. Aqueous solubility of drug is a major factor that determines its dissolution rate. Minimum aqueous solubility of 1% is required to avoid potential solubility limited absorption problems.(Sing, Jan 15,2012)

b) Salt formation

It is one of the common approaches used to increase drug solubility and dissolution rate. It has always been assumed that sodium salts dissolve faster than their corresponding insoluble acids. Eg.sodium and potassium salts of Peniciilin G, sulfa drugs, phenytoin, barbiturates etc. (Sing, Jan 15, 2012)

c) Particle size

There is a direct relationship between surface area of drug and its dissolution rate. Since, surface area increases with decrease in particle size, higher dissolution rates may be achieved through reduction of particle size. Micronization of sparingly soluble drug to reduce particle sizes by no means a guarantee of better dissolution and bioavailability.(Sing, Jan 15,2012)

d) Solid state characteristic

Solid phase characteristics of drug, such as amorphicity, crystallinity, state of hydration and polymorphic structures have significant influence on dissolution rate. (Sing, Jan 15, 2012)

e) Co-precipitation

Dissolution rate of sulfathiazole could be significantly increased by co-precipitating the drug with povidone. (Sing, Jan 15,2012)

2.3.2 Drug product formulation factors

Dissolution rate of pure drug can be altered significantly when mixed with various adjuncts during manufacturing process such as diluents, dyes, binders, granulating agents, disintegrants and lubricants. (Sing, Jan 15, 2012)

2.3.3 Processing factors

a) Method of granulation

Granulation process in general enhances dissolution rate of poorly soluble drug. Wet granulation is traditionally considered superior. But exception is the dissolution profile of sodium salicylate tablets prepared by both wet granulation and direct compression where the dissolution was found more complete and rapid in latter case.(Sing, Jan 15,2012)

b) Compression force

The compression process influence density, porosity, hardness, disintegration time & dissolution of tablet.(Sing, Jan 15,2012)

c) Drug excipient information:

These interactions occur during any unit operation such as mixing, milling, blending, drying, and/or granulating result change in dissolution. (Sing, Jan 15, 2012)

d) Storage conditions

Dissolution rate of Hydrochlorthiazide tablets granulated with acacia exhibited decrease in dissolution rate during 1 yr of aging at R.T. A similar decrease was observed in tablets stored for 14 days at 50- 80ºC or for 4 weeks at 37ºC. (Sing, Jan 15, 2012)

2.3.4 Factors relating dissolution apparatus

a) Agitation

Relationship between intensity of agitation and rate of dissolution varies considerably acc. to type of agitation used, the degree of laminar and turbulent flow in system, the shape and design of stirrer and physicochemical properties of solid.

Speed of agitation generates a flow that continuously changes the liq/solid interface between solvent and drug. In order to prevent turbulence and sustain a reproducible laminar flow, which is essential for obtaining reliable results, agitation should be maintained at a relatively low rate.

Thus, in general relatively low agitation should be applied.

I. Basket method- 100 rpm

II. Paddle method- 50-75 rpm. (Sing, Jan 15, 2012)

b) Stirring element alignment
The USP / NF XV states that the axis of the stirring element must not deviate more than 0.2 mm from the axis of the dissolution vessel which defines centering of stirring shaft to within ±2 mm.

Studies indicant that significant increase in dissolution rate up to 13% occurs if shaft is offset 2-6 mm from the center axis of the flask.

Tilt in excess of 1.5 0 may increase dissolution rate from 2 to 25%. (Sing, Jan 15, 2012)

c) Sampling probe position and filter
Sampling probe can affect the hydrodynamic of the system & so that change in dissolution rate.

For position of sampling, USP / NF states that sample should be removed at
approximately half the distance from the basket or paddle to the dissolution medium and not closer than 1 cm to the side of the flask.

Filter material must be saturated with the drug by repeated passage to avoid losses that might go undetected during the test sampling.

Accumulation of the particulate matter on the surface may cause significant error in the dissolution testing. (Sing, Jan 15, 2012)

2.3.5 Factors relating dissolution test parameters

a) Temperature
Drug solubility is temperature dependent, therefore careful temperature control during dissolution process is extremely important. Generally, a temp of 37º ± 0.5 is maintained during dissolution determination of oral dosage forms and suppositories. However, for topical preparations temp as low as 30º and 25º have been used. (Sing, Jan 15, 2012)

b) Dissolution medium
It is very imp factor affecting dissolution and is itself affected by number of factors such as:

Effect of pH, Volume of dissolution medium and sink conditions, Deaeration of dissolution medium. (Sing, Jan 15, 2012)

2.4 Aim and objective of the study:

Atorvastatin is a widely used lipid lowering agent. In the research some prescriptions of recent time were gone through. It was seen that atorvastatin had been suggested along with omeprazole, ramipril at a time in a particular part of a day,usually after dinner. The main aim or objective of this study is to see if dissolution of atorvastatin is influenced by these drugs.

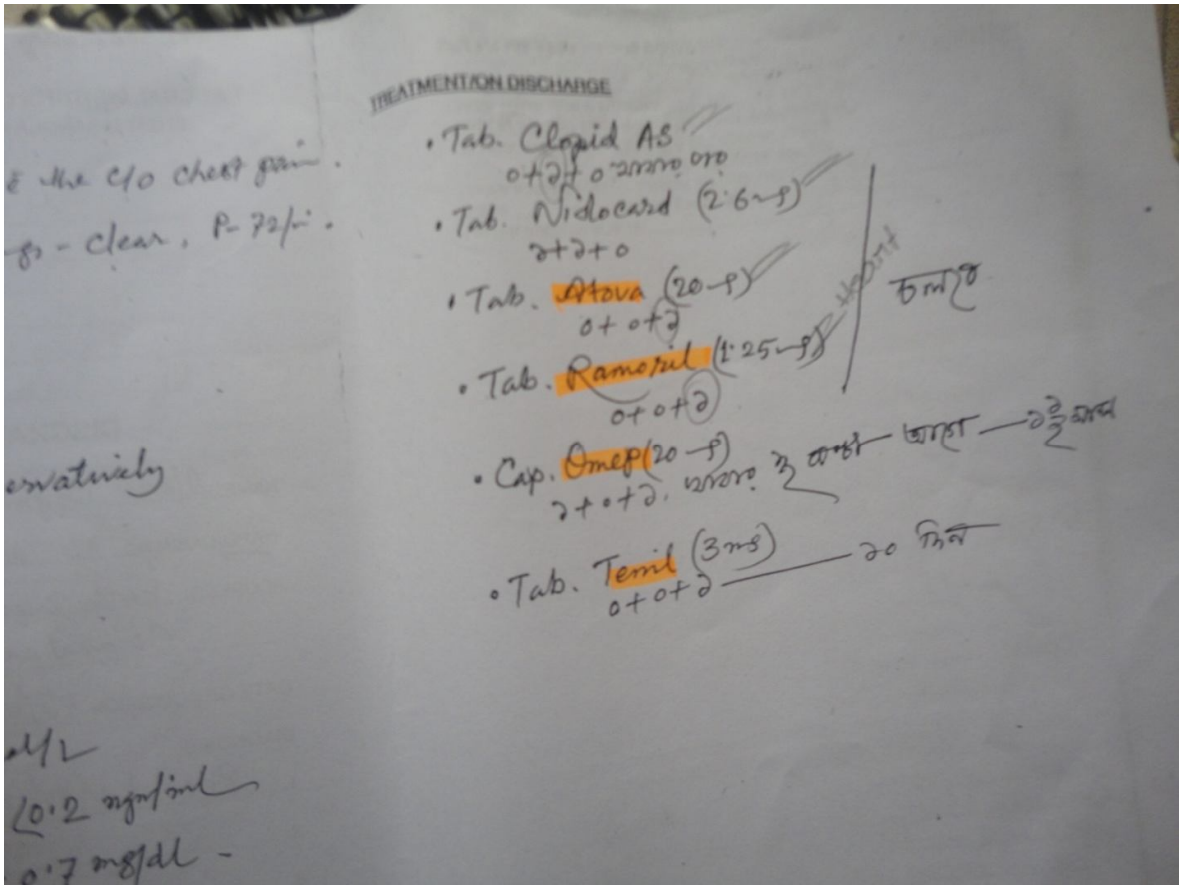


Fig4: Prescription1

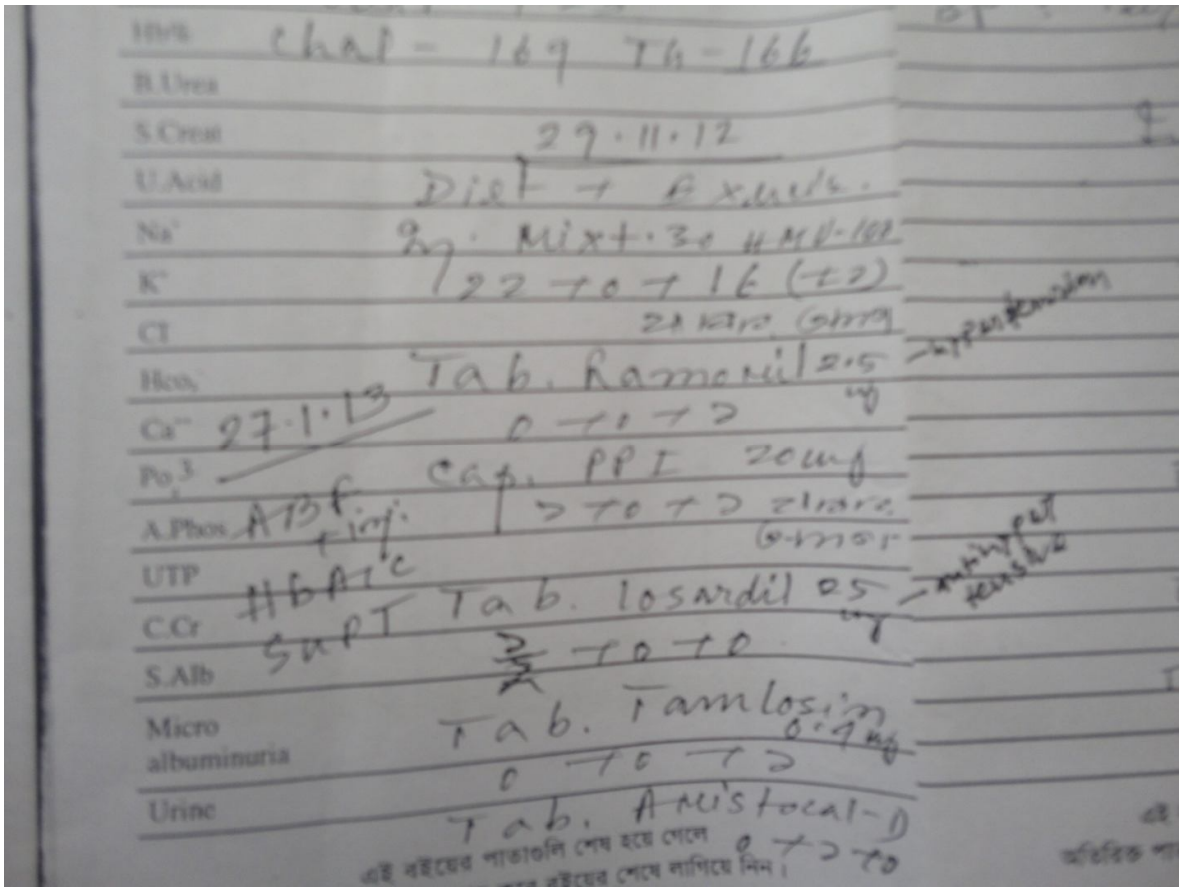


*Fig5:*Prescription2

Several journal, research paper, books were studied on atorvastatin's combination therapy, it's adverse effects, its new kind of therapeutic use. But no such study on atorvastatin's basic pharmacokinetic property influenced by other drugs suggested at a time in a particular part of a day was seen. So this study was a topic of interest. This research work was also aimed to have an *in-vitro* study on atorvastatin's dissolution rate individually, that is how well and fast this drug is dissolved in our body. Again this study served the purpose of studying atorvastatin's *in-vitro* dissolution study when this drug is taken with combination of omeprazol and ramipril. Finally we could compare the different dissolution rate results.

2.5 Significance of our study:

Running atorvastain under dissolution test individually and in combination with omeprazole and ramipril followed by absorbance of both the studies it shows the various dissolution rate results of atorvastatin both individually and in combination at different time intervals. From the study both qualitative and quantitative results can be achieved. Quantitatively this study can show the dissolution rate of atorvastatin individually and when it's taken along with omeprazol and ramipril and qualitatively the study showed if atorvastatin's dissolution which is an important factor of a drug's pharmacokinetic property is influenced by its combination

with the drugs mentioned.If dissolution rate of atorvastatin changes with the combination then it should be further studied that if it has any effect on therapeutic use of drug, or has any harmful effect on patient. According to the finding of these questions dosage schedule of atorvastatin can be modified or the combination of ramipril and omeprazol can be changed if required. Both qualitative and quantitative measurement can lead us to some important facts about the drug;atorvastatin.

Chapter three: Literature Review

3.1 Combination Therapy with Atorvastatin and Amlodipine Suppresses Angiotensin II-Induced Aortic Aneurysm Formation

Abstract

Background

Abdominal aortic aneurysm (AAA) is a life-threatening vascular disease. It is controversial whether statin and calcium channel blockers (CCBs) has an inhibitory effect on the expansion of AAA. Some studies reported that CCBs have an inhibitory effect on Rho-kinase activity. Rho-kinase plays an important role in the pathogenesis of various cardiovascular diseases. However, there is no study reporting of the association between Rho-kinase and human AAAs.

Methods and Results

Experimental AAA was induced in Apolipoprotein E-deficient ($ApoE^{-/-}$) mice infused with angiotensin II (AngII) for 28 days. They were randomly divided into the following 5 groups; saline infusion alone (sham), AngII infusion alone, AngII infusion plus atorvastatin (10 mg/kg/day), AngII infusion plus amlodipine (1 mg/kg/day), and AngII infusion plus combination therapy with atorvastatin (10 mg/kg/day) and amlodipine (1 mg/kg/day). The combination therapy significantly suppressed AngII-induced increase in maximal aortic diameter as compared with sham, whereas each monotherapy had no inhibitory effects. The combination therapy significantly reduced AngII-induced apoptosis and elastin degradation at the AAA lesion, whereas each monotherapy did not. Moreover, Rho-kinase activity, as evaluated by the extent of phosphorylation of myosin-binding subunit (a substrate of Rho-kinase) and matrix metalloproteinase activity were significantly increased in the AngII-induced AAA lesion as compared with sham, both of which were again significantly suppressed by the combination therapy. In human aortic samples, immunohistochemistory revealed that the activity and expression of Rho-kinase was up-regulated in AAA lesion as compared with abdominal aorta from control subjects.

Conclusions

Rho-kinase is up-regulated in the aortic wall of human AAA. The combination therapy with amlodipine and Atorvastatin, but not each monotherapy, suppresses AngII-induced AAA formation in mice in vivo, for which Rho-kinase inhibition may be involved. (Takahashi, Matsumoto mail & Do.e, 2013, Aug 13)

3.2 Atorvastatin and sildenafil lower blood pressure and improve endothelial dysfunction, but only atorvastatin increases vascular stores of nitric oxide in hypertension.

Abstract

Nitric oxide (NO)-derived metabolites including the anion nitrite can recycle back to NO and thus complement NO formation independent of NO synthases. While nitrite is as a major vascular storage pool and source of NO, little is known about drugs that increase tissue nitrite concentrations. This study examined the effects of atorvastatin or sildenafil, or the combination, on vascular nitrite concentrations and on endothelial dysfunction in the 2 kidney-1 clip (2K1C) hypertension model. Sham-operated or 2K1C hypertensive rats were treated with vehicle, atorvastatin (50 mg/Kg), sildenafil (45 mg/Kg), or both for 8 weeks. Systolic blood pressure (SBP) was monitored weekly. Nitrite concentrations were assessed in the aortas and in plasma samples by ozone-based reductive chemiluminescence assay. Aortic rings were isolated to assess endothelium-dependent and independent relaxation. Aortic NADPH activity and ROS production were evaluated by luminescence and dihydroethidium, respectively, and plasma TBARS levels were measured. Aortic nitrotyrosine staining was evaluated to assess peroxynitrite formation. Atorvastatin and sildenafil, alone or combined, significantly lowered SBP by approximately 40 mmHg. Atorvastatin significantly increased vascular nitrite levels by 70% in hypertensive rats, whereas sildenafil had no effects. Both drugs significantly improved the vascular function, and decreased vascular NADPH activity, ROS, and nitrotyrosine levels. Lower plasma TBARS concentrations were found with both treatments. The combination of drugs showed no improved responses compared to each drug alone. These findings show evidence that atorvastatin, but not sildenafil, increases vascular NO stores, although both drugs exert antioxidant effects, improve endothelial function, and lower blood pressure in 2K1C hypertension. (Guimarães,Rizzi &Ceron, 2013 Nov 17)

3.3 Cardio protective Effects of Atorvastatin plus Trimetazidine in Percutaneous Coronary Intervention.

Abstract

Objective: To explore the effects of preoperative administration of conventional doses of atorvastatin plus trimetazidine on the myocardial injury of patients during the perioperative period of percutaneous coronary intervention (PCI).

Methodology: 475 cases of acute coronary syndrome patients before PCI were randomly divided into the control group (238 cases) and experimental group (237 cases).The control group was treated with conventional doses of atorvastatin calcium (20 mg each time, once a night), and the experimental group was treated with conventional doses of atorvastatin calcium plus trimetazidine hydrochloride (20 mg each time, tid) for 3 d. After PCI, preoperative and postoperative 24 h concentrations of serum creatine kinase MB isoenzyme (CK-MB), cardiac troponin I (cTnI) and high sensitivity C-reactive protein (hs-CRP) as well

as activity of myeloperoxidase (MPO) were investigated. Left ventricular ejection fractions of the patients were then examined 4 weeks later.

Results: Postoperative 24 h cTnI concentration and elevated MPO activity of the experimental group were significantly lower than those of the control group (P <0 05). CK-MB activities and hs-CRP concentrations of the two groups did not differ significantly (P> 0 05). Conclusion: The administration of conventional doses of atorvastatin plus trimetazidine three days before PCI is able to protect the perioperative patients from myocardial injury. (Lin,Ma&Zhang , 2013 Apr 29)

3.4 Anti-inflammatory effect of amlodipine plus atorvastatin treatment on carotid atherosclerosis in zucker metabolic syndrome rats.

Abstract

To investigate the effects of amlodipine in combination with atorvastatin on carotid atherosclerotic changes in metabolic syndrome, 8-week-old Zucker fatty rats were treated with vehicle, amlodipine, atorvastatin, or amlodipine in combination with atorvastatin for 28 days. Histological studies of common carotid arteries showed that lipid deposition determined by Sudan III staining was significantly reduced in rats treated with amlodipine or atorvastatin alone and was further reduced by amlodipine in combination with atorvastatin. Immunohistochemical studies of the pro-inflammatory cytokine tumor necrosis factor (TNF)-α, the arterial calcification initiator bone morphogenetic protein (BMP) 2, the angiogenic factor Notch1, and the smooth muscle cell marker α-smooth muscle actin (SMA) showed that the high expression of all four protein in vehicle-treated rats was greatly decreased by amlodipine, atorvastatin, or amlodipine in combination with atorvastatin, in ascending order. Double immunostaining showed marked colocalization of TNF-α with bone morphogenetic protein 2 and Notch1 with α-SMA in the vehicle group, which was greatly reduced by amlodipine plus atorvastatin. These data suggest that combination therapy may be more effective in preventing atherosclerotic processes and subsequent carotid vascular events than administrating amlodipine or atorvastatin alone in metabolic syndrome. **(**Zhang,Tian & Kawai, 2012 Dec 3)

3.5 Rhabdomyolysis Causing AV Blockade Due to Possible Atorvastatin, Esomeprazole, and Clarithromycin Interaction

Abstract

Objective

To report rhabdomyolysis (RML) causing third-degree atrioventricular block secondary to a possible interaction between atorvastatin, esomeprazole, and clarithromycin.

Case summary

A 51-year-old white woman presented to the emergency department with severe weakness, near syncope, shortness of breath, and chest pain. On admission, her electrocardiogram demonstrated bradycardia (40 beats/min) and third-degree heart block. A creatine kinase (CK) level was >7000 U/L. Her medication history was significant for long-term use of atorvastatin (>1 y), a 6-week history of esomeprazole use, and three 500-mg doses of clarithromycin just prior to admission. Her symptoms of weakness, shortness of breath, and chest pain coincided with starting the esomeprazole. During her hospitalization, the woman required pacemaker placement and her CK continued to rise to >40 000 U/L. Screening for other causes of RML, such as thyrotoxicosis, infection, and immune or hepatic diseases, was negative. She gradually improved over a 26-day hospitalization.

Discussion

This is a case of RML resulting in third-degree atrioventricular blockade. An objective causality assessment of the adverse reaction via the Naranjo probability scale revealed a probable association with atorvastatin and a possible association with esomeprazole and clarithromycin. The pharmacokinetic profiles of these agents suggest that a possible contribution to this reaction was P-glycoprotein (PGP) inhibition by esomeprazole altering atorvastatin's normally significant first-pass clearance.

Conclusion

PGP drug interactions with atorvastatin and other hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) may be associated with unreported risks for RML. Further investigation into PGP impact on HMG-CoA appears warranted. (Sipe, Jones & Bokhar, 2011)

3.6 Effect of Atorvastatin on Cyclosporine Pharmacokinetics in Liver Transplant Recipients

Abstract

Background

The development of hyperlipidemia after liver transplant is frequently treated with hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) such as atorvastatin. As atorvastatin and the primary immunosuppressant drug, cyclosporine, are metabolized by the same pathway, there is the potential for an interaction.

Objective

To determine the effect of atorvastatin on cyclosporine pharmacokinetics in liver transplant recipients.

Methods

Six stable, long-term adult liver transplant recipients from a single center who developed posttransplant dyslipidemia were recruited to participate in a 14-day, open-label study of atorvastatin 10 mg/d co administered with standard posttransplant immunosuppression using constant oral doses of cyclosporine and corticosteroids. A 10-point pharmacokinetic profile was performed prior to and on day 14 after commencement of atorvastatin therapy. Cyclosporine concentrations were measured by HPLC-electrospray-tandem mass spectrometry. The AUC was calculated by the linear trapezoidal rule, with other parameters determined by visual inspection.

Results

Atorvastatin coadministration increased the cyclosporine AUC by 9% (range 0–20.6%; 3018 vs 3290 ng•h/mL; $p = 0.04$). No significant change was evident for other cyclosporine pharmacokinetic parameters. Total cholesterol and low-density lipoprotein cholesterol levels were significantly lower on day 14 than at baseline ($p < 0.02$). One patient developed a twofold increase in transaminases after 2 weeks of atorvastatin therapy, but no other clinical or biochemical adverse events were recorded.

Conclusion

Atorvastatin coadministration increases the cyclosporine AUC by approximately 10% in stable liver transplant recipients. This change in systemic exposure to cyclosporine is of questionable clinical significance. Atorvastatin is effective in reducing cholesterol levels in liver transplant recipients. (Taylor, Kubler & Lynch, 2011)

3.7 Absence of Clinically Relevant Interactions between Rivaroxaban An Oral, Direct Factor Xa Inhibitor And Digoxin or Atorvastatin in Healthy Subjects

Abstract

Objective

To investigate potential interactions between rivaroxaban, an oral direct Factor Xa inhibitor approved for the management of thromboembolic disorders, and digoxin or atorvastatin.

Methods

Two randomized, phase 1 clinical trials were undertaken in healthy men to assess pharmacokinetic and pharmacodynamic interactions between rivaroxaban and digoxin or atorvastatin, and the safety of these drug combinations.

Results

Steady-state rivaroxaban did not affect the pharmacokinetic profile of steady-state digoxin (n = 17). Digoxin did not significantly influence the pharmacokinetic profile of single-dose rivaroxaban and had minimal effects on rivaroxaban-induced inhibition of Factor Xa activity and prolongation of clotting time. Similarly, steady-state atorvastatin did not affect the pharmacokinetic profile or the pharmacodynamics of rivaroxaban and vice versa (n = 19). All drugs (alone or in combination) were well tolerated.

Conclusion

There were no clinically relevant pharmacokinetic or pharmacodynamic interactions between rivaroxaban and digoxin, or between rivaroxaban and atorvastatin, suggesting that rivaroxaban can be coadministered with either drug. This study also confirmed that rivaroxaban does not interact with substrates for permeability (P)-glycoprotein alone (digoxin) or P-glycoprotein and cytochrome P_{450} (CYP) 3A4 (atorvastatin). (Kubitza, Becka & Roth; 2011)

3.8 Possible Increase in Liver Enzymes Secondary to Atorvastatin and Black Cohosh Administration.

Abstract

Introduction

Since the publication of the Women's Health Initiative (WHI) trials, there has been a decline in the use of hormonal replacement therapy (HRT). The risks outweighed the benefits in the WHI trials, and therefore women are seeking alternative treatments including herbal remedies to HRT for mitigation of postmenopausal conditions. The authors report a case of drug-herb interaction between black cohosh (Cimicifuga racemosa) and atorvastatin leading to elevation in liver enzymes.

Case summary

A 53-year-old woman with a past medical history significant for atypical chest pain, family history of coronary artery disease, and menopause discontinued oral HRT and started black cohosh for treatment of her menopausal symptoms. The patient also reported taking atorvastatin, aspirin, glucosamine/chondroitin, and vaginal estradiol (Vagifem ®). Routine lab results revealed an acute elevation of her liver enzymes. At this time, additional blood tests were performed to rule out other plausible causes of acute elevation in liver enzymes, which did not reveal other etiologies. It was recommended that she discontinue the black cohosh immediately due to a potential drug-herb interaction. Following the patient's discontinuation of black cohosh, her liver enzymes decreased within 1 week and completely returned to normal within 1 month.

Discussion

Several case reports have associated black cohosh with hepatotoxicity. It was reported that a commercially available formulation of black cohosh may potently inhibit human cytochrome (CYP) 3A4. Inhibition of CYP3A4 by black cohosh could possibly elevate levels of atorvastatin, causing an elevation of liver enzymes. To the authors' knowledge, they report the first case report of drug-herb interaction with use of the black cohosh and atorvastatin. Conclusion: The use of black cohosh concomitantly with atorvastatin may potentially lead to a drug-herb interaction resulting in an elevation of liver enzymes. According to the Naranjo probability scale, there was a possible drug-induced adverse event. Black cohosh should not be routinely recommended for treatment of menopausal symptoms. However, if a patient chooses to use black cohosh against medical advice, particular attention should be given to the potential CYP3A4 drug interactions. (Patel & Derkits ; 2011)

Chapter four: Materials and Methods

4.1 Standards for tests according to US FDA:

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Temp.	Date Updated
Atorvastatin Calcium	Tablet	II (Paddle)	75	0.05 M Phosphate buffer, pH 6.8	900	5, 10, 15 and 30	37±0.5°C	01/15/2004

Table6: Standards for tests according to US FDA

4.2 Materials required:

1. Disodium hydrogen orthophosphate anhydrous (28.40 g)

2. Potassium dihydrogen orthophosphate

3. Atorvastatin tablet (Lipicon10 mg;6 tablets)

4. Omeprazol (Cosec BP 20 mg; 6 tablets)

5. Ramipril (Ramoril 2.5 mg;6 tablets)

6. Water

7. Concentrated HCl (as needed)

8. Liquid 0.1N NaOH.

4.3 Instruments required

1. Dissolution tester. (Paddle-II) (Model DS 8000, Labindia)

2. Weight Balance (APX 224)

3. pH Meter

4. Filter Paper

5. Testubes

6. Glass rod

7. Saucepan

8. Shyringe

9. Beaker

10. Spatula

11. Morter and pastel

12. Volumetric flask

13. Measuring cylinder

14. Spectrophotometer (Shimazdu UV spectrophotometry, UV1800)

Fig.6: Dissolution tester

Fig.7: Weight balance

Fig.8: p^H meter

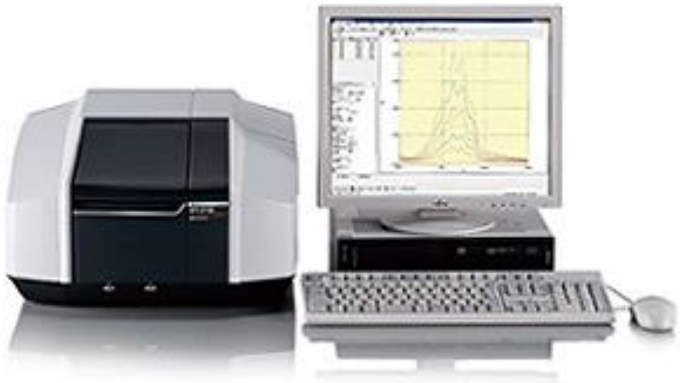


Fig.9: The Spectrophotometer.

4.4 Method:

4.4.1 Preparation of Phosphate Buffer pH 6.8:

For this British Pharmacopoeia was followed; Volume V; Appendices; Appendix I D. Buffer Solution.

Procedure: We Dissolved 28.40 g of disodium hydrogen orthophosphate anhydrous in 1000 ml distilled water that is stock solution A and 11.45 g of potassium dihydrogen orthophosphate in 100 ml distilled water as well that is stock solution B. Then we took 920 ml of stock solution A and 80 ml of stock solution B. Mixed them well. Adjusted the p^H as 6.8 with a calibrated p^H meter. For lowering the pH concentrated HCl was used and for increasing the pH 0.1 N NaOH. (British Pharmacopoeia, 2012 online)

4.4.2 Recommended procedure:

It was ensured that the equipment had been calibrated within the past 6-12 months. The 900 ml buffer solution was placed in each vessel of dissolution tester; the apparatus were assembled and was placed in the water-bath; the temperature of the dissolution medium was allowed to reach 37±0.5°C and remove the thermometer.

Each tablet of the preparation to be tested was allowed to sink to the bottom of each vessel before starting the rotation of the blade, taking care that no air bubbles are present on the

surface of the dosage form. Immediately started rotation of the blade or basket at the rate of 75 rpm.

5ml sample was withdrawn from a zone midway between the surface of the dissolution medium and the top of the rotating blade or basket, not less than 10 mm below the surface and at least 10 mm from the vessel wall at the time intervals of 5, 10, 15 and 30 min; from each vessel. The dissolution medium was replaced instantly with a fresh buffer solution equal to the volume of dissolution medium removed with a help of a syringe of 5ml.

For filtration of the removed liquid as the final stage an inert filter paper was used because it does not cause significant adsorption of the active ingredient from the solution, and does not contain substances extractable by the dissolution medium that would interfere with the specified method of analysis.

Finally absorbance was taken of the filtered liquid with double ray absorbance system.

Chapter five: Results

5.1Data

Time Interval	Tab1	Tab2	Tab3	Tab4	Tab5	Tab6	Average of absorbance
5min	0.032	0.021	0.022	0.028	0.017	0.021	0.024
10min	0.025	0.025	0.015	0.037	0.044	0.035	0.0302
15min	0.061	0.076	0.099	0.044	0.183	0.019	0.0803
30min	0.370	0.490	0.421	0.454	0.399	0.347	0.414

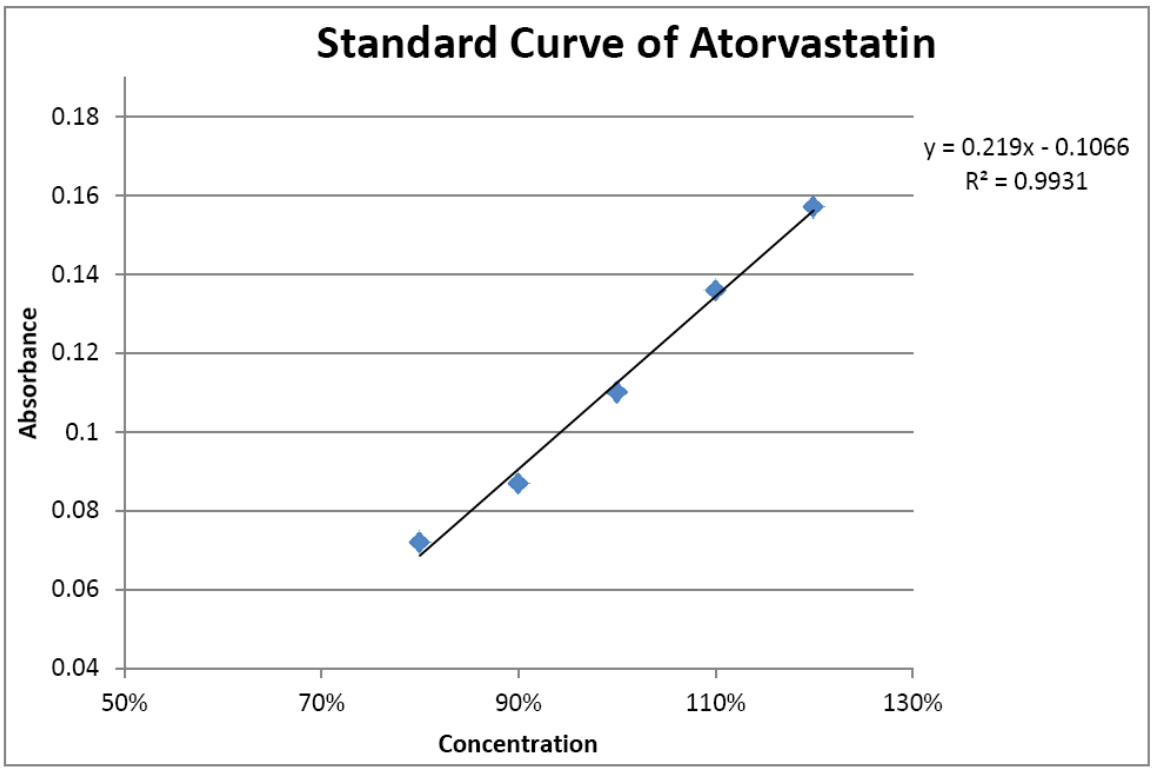
Table7: Absorbance of Atorvastatin (Lipicon 10mg)

Time Interval	Comb. of Tab1	Comb. of Tab2	Comb. of Tab3	Comb. of Tab4	Comb. of Tab5	Comb. of Tab6	Average of absorbance
5min	0.062	0.045	0.076	0.048	0.061	0.059	0.058
10min	0.091	0.111	0.175	0.153	0.088	0.203	0.136
15min	0.240	0.354	0.286	0.184	0.332	0.835	0.371
30min	0.742	0.694	0.483	0.685	0.936	0.834	0.729

Table8: Absorbance of combination of Atorvastatin (Lipicon 10mg) ,Omeprazol (Cosec BP 20 mg), Ramipril (Ramoril 2.5 mg)

Concentration	Absorbance
80%	0.072
90%	0.087
100%	0.11
110%	0.136
120%	0.157

Table9: Absorbance Test of different concentrations of Standard



Graph1: Standard Curve of Atorvastatin

Equation of Percent Dissolve:

$$\text{Dissolution \%} = \frac{AS \times Wst \times 900 \times P}{Ast \times 100 \times \text{Dose of tablet}} \times 100\ \%$$

Where,

AS = Absorbance of sample

A_{st} = Absorbance of standard (0.11)

P = Potency of standard = 97%

W_{st} = weight of standard (0.11mg)

Equation 2: Percent Dissolve of atorvastatin

$$\text{Dissolution \% of only Atorvastatin after 5min interval} = \frac{AS_5 \times W_{st} \times 900 \times P}{A_{st} \times 100 \times \text{Dose of tablet}} \times 100$$

$$= \frac{0.024 \times 0.11 \times 900 \times 0.97}{0.11 \times 100 \times 10} \times 100\ \%$$

$$= 2.093\%$$

$$\text{Dissolution \% of Atorvastatin with Omeprazol and ramipril after 5min interval} = \frac{AS_5 \times W_{st} \times 900 \times P}{A_{st} \times 100 \times \text{Dose of tablet}} \times 100$$

$$= \frac{0.058 \times 0.11 \times 900 \times 0.97}{0.11 \times 100 \times 10} \times 100\%$$

$$= 5.063\%$$

$$\text{Dissolution \% of only Atorvastatin after 10min interval} = \frac{AS_{10} \times W_{st} \times 900 \times P}{A_{st} \times 100 \times \text{Dose of tablet}} \times 100\%$$

$$= \frac{0.0302 \times 0.11 \times 900 \times 0.97}{0.11 \times 100 \times 10} \times 100\%$$

$$= 2.64\%$$

$$\text{Dissolution \% of Atorvastatin with Omeprazol and ramipril after 10min interval} = \frac{AS_{10} \times W_{st} \times 900 \times P}{A_{st} \times 100 \times \text{Dose of tablet}} \times 100\%$$

$$= \frac{0.136 \times 0.11 \times 900 \times 0.97}{0.11 \times 100 \times 10} \times 100\%$$

$$= 11.872\%$$

$$\text{Dissolution \% of only Atorvastatin after 15min interval} = \frac{AS_{15} \times W_{st} \times 900 \times P}{A_{st} \times 100 \times \text{Dose of tablet}} \times 100\%$$

$$= \frac{0.0803 \times 0.11 \times 900 \times 0.97}{0.11 \times 100 \times 10} \times 100\%$$

=7.01 %

Dissolution % of Atorvastatin with Omeprazol and ramipril after 15min interval = $\frac{AS_{15} \times W_{st} \times 900 \times P}{A_{st} \times 100 \times \text{Dose of tablet}} \times 100\%$

$$= \frac{0.371 \times 0.11 \times 900 \times 0.97}{0.11 \times 100 \times 10} \times 100\%$$

=32.38%

Dissolution % of only Atorvastatin after 30min interval = $\frac{AS_{30} \times W_{st} \times 900 \times P}{A_{st} \times 100 \times \text{Dose of tablet}} \times 100\ \%$

$$= \frac{0.414\times0.11\times900\times0.97}{0.11\times100\times10}\times100\%$$

=36.14%

Dissolution % of Atorvastatin with Omeprazol and ramipril after 30min interval= $\frac{AS_{30}\times W_{st}\times900\times P}{A_{st}\times100\times\text{Dose of tablet}}\times100\%$

$$= \frac{0.729\times0.11\times900\times0.97}{0.11\times100\times10}\times100\%$$

= 63.641%

5.2 Result:

Comparing the percent dissolution result of only Atorvastatin with that of the combination of Atorvastatin, Omeprazol and Ramipril regarding 5min,10min,15min and 30min interval; every time it showed that dissolution rate of the combination is greater than that of Atorvastatin alone. After 5min, 10min, 15min and 30min dissolution rate of atorvastatin was 2.093%,2.64%,7.01%,36.14% respectively, and for the combination these were 5.063%,11.872%,32.38%,63.641% respectively. Hence Administering Atorvastatin with the combination of Omeprazol and Ramirpil increased the dissolution rate of Atorvastatin.

Chapter six: Discussion

Atorvastatin is a lipid lowering drug with Absorption 30%,Bioavailabilty 12% ,Hepatic extraction 70% ,Protein binding >98%, Half life 7-20. These properties of Atorvastatin have been often showed to change by influence of various drugs taken in combination with Atorvastatin. Some studies have been done on effect of various drugs on Atorvastatin. Some of them are:

Effect of CYP3A4 inhibitors:

Simvastatin, lovastatin, and atorvastatin are metabolized by cytochrome P450 (CYP) 3A4 (simvastatin acid is also metabolized by CYP2C8); their plasma concentrations and risk of myotoxicity are greatly increased by strong inhibitors of CYP3A4 (eg, itraconazole and ritonavir). Weak or moderately potent CYP3A4 inhibitors (eg, verapamil and diltiazem) can be used cautiously with small doses of CYP3A4-dependent statins. (Marks,2013)

Effect of CYP2C9 and CYP2C8 inhibitors:

Potent inhibitors of CYP2C9 can increase plasma concentrations of fluvastatin. (Marks,2013)

Effect of inducers:

Rifampin (INN, rifampicin) and other potent inducers of CYP enzymes can greatly decrease the AUC of statins that are metabolized by CYP3A4. The mean AUC of simvastatin acid was reduced by 94% by rifampin and by 82% by carbamazepine. (Marks,2013)

Membrane transport:

OATP1B1 seems to be one of the most important membrane transporters that mediate the uptake of statins into the liver, and certain drugs can affect its activity. In addition, many statins are substrates of other efflux or uptake transporters, expressed in the intestine, liver, or kidneys—for example, MDR1, MRP2, BCRP, OATP1B3, OATP2B1, and OAT3. These transporters also may mediate drug interactions.

Some other studies like Effect of fibrates, Effect of cyclosporine. (Marks, 2013)

Ramirpil is a potent calcium channel blocker and Omeprazol is a potent proton pump inhibitor. No study regarding the effect of these kinds of drugs on Atorvastatin was noticed. It was a different study where the result showed that dissolution rate of Atorvastatin taken with combination of Ramipril and Omeprazol is greater than that of Atorvastatin individually. After 5min, 10min, 15min and 30min dissolution rate of atorvastatin was 2.093%,2.64%,7.01%,36.14% respectively, and for the combination these were 5.063%,11.872%,32.38%,63.641% respectively .The amount of increase with time interval of 5min,10min,15min and 30 min. With every time interval dissolution rate of atorvastatin individual and with combination increases. The difference of these values increases with time as well. It’s just a finding which should be further studied that if this increased dissolution rate is useful for therapeutic use. It also should be studied if it’s useful how the dosage regimen should be adjusted according different patient’s need.

Chapter seven: Conclusion

Drug-Drug interaction is an age old topic of study or concern of pharmacist for adjusting dose of drugs or for preferable choice of drugs. This study showed how drug-drug interaction between Atorvastatin, Omeprazol and Ramipril affected the dissolution rate of Atorvastatin. The dissolution rate of atorvastatin increases when it's taken along with omeprazol and ramipril. This study can be further proceeded by experimenting this combination of different patient and observing if this increased dissolution rate of Atorvastatin has any effect on patient body. While prescribing Atorvastatin with this combination this increase of it's dissolution rate must be considered by pharmacist. Advantage and disadvantage regarding Atorvastatin should be studied more if it is caused by the increase of dissolution rate of this drug when it's taken with this combination.

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