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IMPROVING THE BIOAVAILABILITY OF ATORVASTATIN CALCIUM: FORMULATING TABLETS FROM SOLID DISPERSIONS WITH PVP K30 AND HPMC K4M

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ABSTRACT

This study aims to enhance the solubility and dissolution rate of atorvastatin calcium, a poorly water-soluble drug, by formulating solid dispersions. The objectives include Investigating the impact of different carriers (e.g., polymers, surfactants) on atorvastatin calcium solubility characterizing the physicochemical properties of the prepared solid dispersions (e.g., drug-carrier interactions, crystallinity) Developing and evaluating tablets containing the optimized solid dispersion; and comparing the in vitro drug release profile of the developed tablets with a marketed atorvastatin calcium formulation. The successful development of these solid dispersions could potentially improve the bioavailability and therapeutic efficacy of atorvastatin calcium.

KEYWORDS

Drug delivery, Atorvastatin calcium, Solid dispersion and Solubility.

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INTRODUCTION

Hyperlipidaemia is a family of disorders characterised by abnormally high levels of lipid (fats) in the blood.

Hyperlipidemia is traditionally defined as conditions in which the concentration of *cholesterol* or *triglyceride-carrying lipoproteins* in plasma exceeds an arbitrary normal limit. These lipoprotein deposits in the interstitial space of arteries arising from the aorta restrict blood supply to the heart. This phenomenon is known as atherosclerosis. Higher deposition of lipoproteins completely blocks the blood supply to the heart, and thus myocardial infarction (MI) occurs, which is commonly known as a heart attack.

CLASSIFICATION OF HYPERLIPIDEMIA

BASED ON THE LIPID TYPE

Hypercholesterolemia **-** The level of cholesterol is elevated.

Hypertriglyceridemia - Elevated level of triglycerides.

BASED ON THE CAUSING FACTOR

Familial (primary) hyperlipidemi

Based on the causing factors hyperlipidemia can be designated as either primary or secondary. According to Fredrickson familial hyperlipidemia is classified into five types based on electrophoresis or ultracentrifugation pattern of lipoprotein.

Type I- Raised cholesterol with high triglyceride levels

Type II- High cholesterol with normal triglyceride level

Type III- Raised cholesterol and triglycerides

Type IV- Raised triglycerides, atheroma and uric acid

Type V- Raised triglycerides

Acquired (secondary) hyperlipidemia

Acquired hyperlipidemia (secondary dyslipoproteinemia) results from an underlying disorder and leads to plasma lipid and lipoprotein metabolism alterations. This type of hyperlipidemia may mimic primary forms of hyperlipidemia and can cause similar consequences. They may result in an increased risk of premature atherosclerosis, pancreatitis and other complications of the chylomicronemia syndrome.

The most common causes of acquired hyperlipidemia are given below.

Diabetes Mellitus

Use of drugs such as diuretics, β-blocker and oestrogens

Alcohol consumption

Some rare endocrine disorders and metabolic disorders

Hypothyroidism

Renal failure

Nephritic syndrome

Major primary and secondary forms of hyperlipidemia their lipoprotein abnormalities and the drugs used for their treatment are listed in the below tables

Hypertension, high lipids and smoking are major CHD risks. LDL-C increases CHD risk, while HDL-C lowers it. Estrogens reduce serum lipids in females.

CAUSE OF HYPERLIPIDEMIA

A diet rich in saturated fat and cholesterol increases blood cholesterol and triglyceride levels.

Other disorders such as obesity, diabetes mellitus and hypothyroidism increase the risk of hyperlipidemia

Smoking and a sedentary lifestyle

Excessive use of alcohol

Certain drugs as steroids and β- blocker

Hereditary factor

SYMPTOMS OF HYPERLIPIDEMIA

Hyperlipidemia usually has no noticeable symptoms and tends to be discovered during routine examinations for atherosclerosis or cardiovascular disease.

Symptoms may include chest pain (angina), heart attack or stroke

When levels are exceedingly high, cholesterol may be deposited in tendons or just beneath the skin under the eye

Swelling of organs such as the liver, spleen or pancreas

Blockage of blood vessels in the brain and heart

Higher rate of obesity and glucose intolerance

Pimple-like lesions across the body

PATHOGENESIS OF HYPERLIPIDEMIA

Lipoproteins transport cholesterol, triglycerides and phospholipids. Elevated TG, LDL-C, and low HDL-C increase CHD risk. Early hyperlipidemia causes monocytes and platelets to attach to damaged vessel walls, triggering plaque formation. Plaque rupture can lead to unstable angina, heart attack, and sudden death.

DIAGNOSIS OF HYPERLIPIDEMIA

Hyperlipidemia has no symptoms and is detected through a lipid profile blood test. The NCEP recommends screening starting at age 20, with repeats every five years if normal.

PREVENTION OF HYPERLIPIDEMIA

A low-fat, low-cholesterol diet, high in soluble fibers, regular exercise, and healthy weight maintenance help manage hyperlipidemia. If lifestyle changes fail, cholesterol-lowering drugs may be needed.

TREATMENT OF HYPERLIPIDEMIA

In 1987, the NIH established the NCEP, led by the ATP, to guide hyperlipidemia testing, evaluation, and treatment. The ATP guidelines set treatment goals based on a patient's CHD risk.

ATP recommends two methods of treatment

Therapeutic lifestyle changes

Initial treatment for mild hyperlipidemia includes diet modification, exercise, smoking cessation, and weight loss, especially for those with fewer risk factors. Diet should limit total fat to 25%-35% of energy, with less than 7% from saturated fats and cholesterol intake under 200mg daily. Plant sterols and soluble fiber can help, potentially reducing cholesterol by 10%-15%.

Drug therapy

High LDL, risk factors, and CHD warrant drug therapy alongside lifestyle changes. Treatment may include statins, ezetimibe, bile acid sequestrants, niacin, fibric acid derivatives and plant sterols. In rare cases, blood plasma removal may be needed. Lifelong management with lifestyle changes and medication is often required.

SOLID DISPERSION

Poor solubility and membrane permeability of many drugs lead to low oral bioavailability. Research focuses on enhancing solubility, dissolution rate, and permeability to improve drug absorption. Solid dispersion (SD) is a key method to improve solubility by dispersing the drug in an inert carrier, like polyethylene glycol (PEG) or polyvinyl pyrrolidone (PVP). This approach has been effective in increasing dissolution and bioavailability, making it a popular, economical solution since the 1960s.

Advantage of solid dispersion

Preparation of solid dispersions results in reduced particle size improved surface area and increased dissolution rate. The ultimate result is improved bioavailability.

Wettability is improved during SD production. Improved wettability results in increased solubility. Here the carriers play a major role in improving the wettability of the particle.

Particles in SDs have a higher degree of porosity. The increased porosity of SD particles accelerates the drug release profile. Increased porosity also depends on carrier properties.

In SD drugs are presented as supersaturated solutions which are considered to be metastable polymorphic forms. Thus, presenting drugs in amorphous form increases the solubility of the particles.

Rapid dissolution rates that increase the rate and extent of the absorption of the drug and a reduction in systemic metabolism both can lead to the need for lower doses of the drug.

Disadvantages of solid dispersion

The major disadvantages of SDs are related to their instability.

Several systems have shown changes in crystallinity and a decrease in dissolution rate with ageing. By absorbing moisture, phase separation, crystal growth or a change from metastable crystalline form to stable form can take place which leads to the reduction of drug solubility.

Moisture and temperature have more of a deteriorating effect on SDs than on physical mixtures. Sometimes it is difficult to handle because of tacking

During formulation sometimes it may form a hard lump which is very difficult to break on a large scale.

LIMITATIONS OF SOLID DISPERSIONS

The physical and chemical stability of drugs and vehicles

Method of preparation, reproducibility of its physiochemical properties

Formulation of solid dispersion into dosage form

Scale-up of manufacturing processes

CLASSIFICATION OF SOLID DISPERSION BASED ON CARRIED USED

First generation

First-generation solid dispersion was prepared using crystalline carriers such as urea and sugar, which were the first carriers to be employed in solid

dispersion. They have the disadvantage of forming crystalline solid dispersion, which is thermodynamically more stable and does not release the drug as quickly as amorphous ones.

Second generation

Second-generation solid dispersions include amorphous carriers instead of crystalline carriers which are usually polymer. These include synthetic polymers such as povidone (PVP), polyethene glycol (PEG) and polymethacrylates as well as natural product-based polymers such as hydroxyl propyl methyl cellulose (HPMC), ethyl cellulose, hydroxyl propyl cellulose or starch derivates like cyclodextrins.

Third generation

Recently, it has been shown that the dissolution profile can be improved if the carrier has surface activity or self-emulsifying properties. Therefore, third-generation solid dispersion appeared. The use of surfactants such as inulin, minutes SP1, capitol 888 ATO, and poloxamer 407 as carriers was shown to be effective in originating high polymorphic purity and enhanced *in-vivo* bioavailability.

BASED ON THE SOLID-STATE STRUCTURE

Exhibiting immiscibility in Fluid State

If a drug and polymer are immiscible in their fluid state, it is expected that they would not exhibit miscibility on the solidification of the fluid mixture. Such systems may be regarded as similar to their corresponding physical mixture and any enhancement in dissolution performance may be owing to modification in morphology of drug and /or polymer due to physical transformation (i.e., solid to liquid state and back), intimate drug-polymer mixing, and/or enhanced surface area.

Drug and polymer exhibiting miscibility in a fluid state

If the drug and polymer are miscible in their fluid state, then the mixture may or may not undergo phase separation during solidification, thereby influencing the structure of solid dispersion

Immiscible in a fluid state

Eutectic mixture

The eutectic mixture was first described as a solid dispersion in 1961 by Sekiguchi & Obi. Eutectic mixtures are formed when the drug and polymer are miscible in their molten state, but on cooling, they crystallize as two distinct components with negligible miscibility. When a drug (A) and a carrier (B) are co-melted at their eutectic composition defined by point 'e', the melting point of the mixture is lower than the melting point of either drug or carrier alone. At the eutectic composition (e), both drug and carrier exist in a finely divided state, which results in a higher surface area and enhanced dissolution rate of the drug. This was first reported for sulfathiazole-urea. Other examples are griseofulvin and tolbutamide in polyethene glycol (PEG-2000).

Crystalline solid dispersion (Crystalline suspension)

A crystalline solid dispersion (or suspension) is formed when the rate at which a drug crystallizes from the drug-polymer miscible mixture is greater than the rate at which drug-polymer fluid mixture solidifies

Amorphous solid dispersion (Glassy suspension)

If the drug-polymer fluid mixture is cooled at a rate that does not allow for drug crystallization, then the drug is kinetically trapped in its amorphous or "solidified-liquid" state. These types of dispersion have the risk of potential for conversion to a more stable and less soluble crystalline form.

Miscible in solid solution

In this system, a homogenous one-phase system is formed when the two components crystallize together. The particle size of the drug is reduced to its molecular size in the solid solution. Thus, a faster dissolution rate is achieved in a solid solution than the corresponding eutectic mixture. Solid solutions can be classified as continuous or discontinuous according to the extent of miscibility of two components.

Continuous solid solution

The components are miscible in all proportions in a continuous solid solution. Hypothetically, this means that the bonding strength between the two components than the bonding strength between the molecules of each of the individual components.

Discontinuous solid solution

The solubility of each of the components in the other components is limited in the case of discontinuous solid solution. One of the solid components is completely dissolved in the other

solid components in these regions. The mutual solubility of two components starts to decrease below a certain temperature. Goldberg reported that the term solid solution should only be applied when the mutual solubility of the two components exceeds 5%.

PREPARATION OF SOLID DISPERSION

Physical mixing method

The known quantity of drug and polymer were weighed separately and passed through sieve No.80. The drug was collected and transferred into a clean and dry glass mortar. The drug and polymer were triturated for 5 minutes and again screened through sieve No. 80. The sieved mixture was collected and packed in a wide-mouthed amber-coloured glass container and was hermetically sealed.

Fusion method

A specified quantity of polymer was taken in a china dish and it was heated at 50°C on a mantle until molten solution was formed. To the molten solution specified quantity of drug was added and triturated vigorously at room temperature. Grind the mass if necessary and it was screened through sieve No. 100. Then the mixture was collected, packed hermetically sealed and stored at an ambient temperature.

Solvent evaporation method

The drug was taken in a china dish and was dissolved in a few ml of solvent. To the solution, a specific amount of polymer was added and the mixture was heated at 50°C on a mantle with continuous stirring until the solvent was evaporated. Then the mixture was collected and packed in amber-coloured glass containers and was hermetically sealed. Then the mixture was stored at ambient conditions.

Lyophilisation

Specific quantities of drug and polymer were weighed and added with a minimum amount of water. This dispersion was rapidly solidified by freeing in a lyophilizer. The solvent in the dispersion was sublimed under a pressure of 10M torr and condensed on a -40°C condenser. After the solvent was completely removed, the powder residue appeared as a porous, light and fluffy mass. The lyophilized preparations were stored in a desiccator at room temperature.

METHODOLOGY

Preformulation study

Preformulation studies involve physical, chemical and biological characterization of new drug substance in order to develop stable, safe and effective dosage form. Preformulation testing encompasses all studies enacted on drug compounds in order to produce useful information for subsequent formulation of a stable and bio-pharmaceutically suitable drug dosage form.

Melting point

Melting point of pure drug was determined by capillary tube method using melting point apparatus. About 10mg of pure drug was filled in one end sealed capillary tubes by tapping method and the temperature at which change in physical state occurred was noticed and determined as the melting point of pure drug

Determination of λ max

Preparation of stock A

10mg of atorvastatin calcium was accurately weighed and dissolved in 1ml of methanol to obtain a drug concentration of 1000mcg/ml

Preparation of stock B

1ml of stock A solution was diluted to 10ml with methanol to obtain a drug concentration of 100mcg/ml

Determination of analytical wavelength

1ml of stock B was diluted to 10ml with methanol then the solution was scanned using double beam UV spectrophotometric in the spectrum mode between the wavelength ranges from 200-400nm.

CALIBRATION CURVE OF ATORVASTATIN CALCIUM

Primary stock solution atorvastatin calcium was prepared by dissolving 10mg of ATC in 10ml of methanol in standard flask. Aliquots of ATC was prepared from stock solution in the concentration range of 2-10ug/ml in 10ml standard flask using methanol as solvent. The absorbance of ATC standard solution was measured at 246nm (max of ATC) against methanol as blank. The standard graph was prepared with concentration of solution (in ug/ml) on X-axis and absorbance on Y-axis.

Solubility study

Pure drug atorvastatin calcium was added to 2ml of various medium like water, pH 7.4 and methanol until solution get saturated. The samples were

centrifuged and filtered through 0.45um membrane filter to separate undissolved drugs. After suitable dilution, the absorbance was measured at 246nm.

FT-IR DRUG POOLYMER COMPATIBILITY STUDY

Drug excipients compatibility was determined by KBr pellet method using Fourier Transform infrared Spectrophotometer A base line correction was made using dried KBr and then spectra of dried mixtures of drug with and without excipients was recorded. The samples were prepared as KBr pellets by compressing at 6 ton/nm2. The wavelength ranges were selected between 400 4000cm-1. (Xingwang Zhang *et al*, 2018).

FORMULATION DEVELOPMENT

Formulation of Atorvastatin calcium solid dispersion

Solid dispersions of atorvastatin calcium were prepared using PVP K30 and HPMC ES in different drug to polymer ratios by solvent evaporation method. Drug: polymer combinations [ratio 1:1:1, 1:2:1,1:3:1,1:4:1, 1:2:2, 1:1.5:1.5] were dissolved in methanol and stirred for 15 minutes at room temperature After complete dissolution, the solvent was removed by using electrical water bath a 70°C. The residues were then pulverized by mortar and pestle, passed through a sieve [mesh size 60] and then stored in desiccators at ambient temperature.

Optimization of polymer concentration

Effect of polymer concentration on solubility of atorvastatin calcium was studied by optimizing various concentration of PVP K 30, HPMC ES. (Shamsuddin FM *et al*, 2016).

CHARACTERISATION OF PREPARED ATORVASTATIN CALCIUM SOLID DISPERSION

Solubility

Prepared solid dispersions were added to 2ml of water, until solution get saturated. The samples were centrifuged and filtered through 0.45µm membrane to separate undissolved drugs. After suitable dilution, the absorbance was measured at 246nm. Based on the solubility studies, optimized batch of solid dispersion was chosen, and it was subjected for further evaluation.

Drug Content

The optimized batch F4 was evaluated for its drug content. 60mg (equivalent to 10mg of ATC) of solid dispersion was dissolved in 100ml of methanol. From this 1ml was taken and made up to 10ml. Further it was diluted to 10ml and the samples were centrifuged. It was filtered through 0.45um membrane and the absorbance was measured at 246nm.

FORMULATION OF ATORVASTATIN CALCIUM TABLET USING OPTIMIZED SOLID DISPERSION

Preparation of granules

The optimized solid dispersion (F4) containing ATC was formulated into tablet by wet granulation method. Accurately weighed solid dispersion containing Atorvastatin calcium was taken. To that specified quantity of diluent and binder solution were added and mixed thoroughly to get wet granules. Granules were then passed through sieve (#10 mesh sieve) and allowed to dry at 60°C in a hot air oven. Dried granules were passed through #20 mesh and magnesium stearate and talc were added. (Wenxiang D *et al*, 2018).

Formulation of Atorvastatin calcium tablets

Dried granules containing atorvastatin calcium was formulated into using RIMEK tables mini press tablet punching machine. It was compressed using 6mm inch. Tablet weight was optimized as 150mg to match with the marketed product. Each tablet contains mg 61.22mg of atorvastatin calcium solid dispersion equivalent to atorvastatin calcium 10mg.

EVALUATION OF ATORVASTATIN CALCIUM TABLET

Weight variation test

Weight variation of atorvastatin calcium tablet was performed using 20 tablets. The tablets were weighed individually using electronic balance. The average weight was calculated and with individual tablets weight was then compared average value and the deviation value was calculated.

Average weight was calculated using following equation.

$$Average\ weight = \frac{\text{Total weight of all the tablets}}{Number\ of\ tablets}$$

$$\%\ deviation = \frac{Actual\ tablet\ weight - average\ weight}{Average\ weight} * 100$$

Friability test

Tablet friability was determined by Remi friability tester. Randomly selected 6 tablets were weighed and placed in the rotating drum which was already programmed with 25rpm for 4 minutes (100 revolution). After the rotation, the tablets were removed, dusts were wiped and weighed again to calculate percentage friability.

$$\text{Percentage friability} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} * 100$$

Hardness test

The Pfizer hardness tester was used for measuring the hardness of formulated atorvastatin calcium tablets, six tablets were taken randomly and subjected to test. The hardness was found to be 4-6kg/cm'.

Disintegration time test

Disintegration test was performed by using Remi Disintegration apparatus. Randomly selected 6 tablets were placed in disintegration apparatus filled with phosphate buffer pH 6.8. The time taken for complete disintegration of tablet was noted.

***In vitro* drug release study**

In vitro drug release studies of marketed and formulated tablet were carried out in Labtronics dissolution test apparatus using specified volume of 900ml dissolution medium maintained at 37°C ± 0.5°C. The tablets were directly placed in the medium and the apparatus was operated at 75rpm. The sample (5ml) was withdrawn at intervals of 10, 20, 30, 40, 50, 60 minutes, replaced with fresh dissolution medium in order to maintain sink condition. After that, samples were analysed using UV spectrophotometer at 246nm respectively. The percentage drug release was calculated which was compared with marketed formulation (Lipvas). (Wenxiang D *et al*, 2018)

Dissolution system

Medium – Phosphate buffer pH7.4
Apparatus -Labtronics
rpm/Temperature – 75rpm/ ± 0.5%
Sampling time -10, 20, 30, 40, 50, 60 minutes

RESULTS AND DISCUSSION

Pre-formulation study

Melting point study

The melting point of ATC were determined by capillary tube method and it was found to be 167°C which confirms the purity of drug.

Determination of λ max

The highest concentration (10ug/ml) was chosen for determination of λ max which shows maximum absorption at 246nm. From the UV Visible spectrum, the max of ATC was found to be 246nm and used for further studies.

CALIBRATION CURVE OF ATORVASTATIN CALCIUM

Standard graph was constructed for various concentration 2-10ug/ml. The absorbance was determined corresponding to their concentration. Correlation coefficient of ATC was found to be r=0.9998 which shows graph was linear.

SOLUBILITY STUDY

Solubility of Atorvastatin calcium in different solvent such as water, Phosphate buffer pH 6.8 and 0.1N HCI. The results show that the atorvastatin calcium was poorly soluble in phosphate buffer.

FT-IR Study

Drug-excipients compatibility was checked by comparing the IR spectra of pure drug, excipients and physical mixture of drug and excipients. FT-IR of drug excipients mixture retained the characteristic functional peaks of drug and it ensured that there was no interaction between the drug and excipients.

CHARACTERISATION OF ATORVASTATIN CALCIUM SOLID DISPERSION

Solubility study of prepared solid dispersions

Solubility study was performed for all the solid dispersion formulation in water. From this, the formulation F4 containing DRUG: PVP K30: HPMC ES ratio of 1:4:1 was found to be favourable one because of its high solubility when compared with pure drug. So, that it was subjected to further evaluations.

Drug Content

The % drug content was found by of the formulation F4 was centrifugation method. The drug Content found to be 98% of ATC. From this it dose of helps to fix the drug which is equivalent to the dose of marketed conventional Atorvastatin formulation. The calcium tablet was formulated by wet technique and its post granulation compression parameters were also evaluated.

EVALUATION OF ATORVASTATIN CALCIUM TABLET

WEIGHT VARIATION TEST

The percentage weight variation for the tablet was performed. All the tablet found to have weight variation as per the Indian pharmacopeia limits (±7.5%).

Friability test

Tablet friability was determined by Remi friability tester. The percentage of friability was found to be 0.56% which is considered as acceptable limit (IP limit) (<1%). This shows formulated tablets can withstand the physical abrasion and mechanical stress.

Hardness test

The hardness of the formulated tablets was determined by Pfizer hardness tester and found in the range of 4.9 to 5.3 which complies IP limits (4-6 Kg/cm) from this prepared tablet ability to withstand the shock of handling, packaging and shipping.

Disintegration test

Disintegration test was performed by using Remi disintegration apparatus and disintegration time was found in the range of 7-12 minutes which complies IP limit. This shows prepared get disintegrated into fine particle which could enhance the solubility of the drug.

Dissolution study

In vitro drug apparatus for prepared release study was carried out by using Labtronics dissolution solid dispersion (F4), its tablet formulation and marketed product (Lipvas*). Among the samples tested, only 90.1% of ATC of marketed product released at 40 minutes. Whereas, when formulation F4 was evaluated, the percentage drug release of ATC was 97.3%. Improvement in dissolution rates of the prepared tablet by hydrophilic and solubilizing effect of PVP K30 in the dissolution medium. This hydrophilic polymer can provide greater dissolution rates by reducing the interfacial tension between the drug particles and the release medium. Due to the particle size reduction and a decrease in the drug crystallinity during the SD preparation process are probable mechanisms that are involved in the enhancement of dissolution rate.

Table No.1: Fredrickson classification for hyperlipidemia

Hyperloop Proteinema	Synonyms	Defect	Increased Lipoprotein	Symptoms	Treatment
Type I (rare)	Familial hyper Chylomic Ronemia	Decreased Lipoprotein Lipase (LPL)	Chilli Microns	Acute pancreatitis, Lipemiaretinalis, Xanthomas, hepatic Splenomegaly	Diet control
	Familial Apoprotein CII deficiency	Altered ApoC2			
		LPL inhibitor in blood			
Type II	Familial hypercholesterolemia	LDL receptor deficiency	LDL receptor deficiency	Xanthelasma, Arcussenilis, tendon xanthomas	Bile acid sequestrants, statins, niacin
	Familial	Decreased LDL	LDL and		Statins,

	combined hyperlipidemia	receptor and increased ApoB	VLDL		niacin, Fibrates
Type III (rare)	Familial Dysbetalipo proteinemia	Defeat in Apo E2 synthesis	IDL	Tuboruptive xanthomas and palmar xanthomas	Fibrate, statins
Type IV	Familial hyper Triglyceridemia	Increased VLDL production and decreased elimination	VLDL	Can cause pancreatitis at high triglyceride levels	Fibrate, niacin, statins
Type V (rare)	Endogenous hyper Triglyceridemia	Increased VLDL production and decreased LPL	VLDL and chylomicrons		Niacin, Fibrate

Table No.2: Common forms of primary hyperlipidemia

S.No	Disorder	Lipoprotein abnormality	Drug therapy
1	Familial hypercholesterolemia	↑↑LDL	Lovastatin
2	Familial defective apolipoprotein B	↑↑LDL	None
3	Polygenic hypercholesterolemia	↑LDL	Lovastatin
4	Familial hypercholesterolemia	↑Chylomicrons	Nicotinic acid
5	Familial lipoprotein lipase deficiency	↑VLDL	Gemfibrozil
6	Familial combined hyperlipidemia	↑VLDL, ↑LDL, ↑HDL	Nicotinic acid
7	Familial dysbetalipoproteinemia	↑Chylomicrons, ↑LDL, ↓IDL, ↓HDL	Gemfibrozil

Table No.3: Common forms of secondary hyperlipidemia

S.No	Condition	Lipid abnormalities	Lipoprotein abnormalities
1	Diabetes mellitus	↑TG	↑VLDL, ↓HDL
2	Nephritic syndrome	↑Chol	↑LDL
3	Uraemia	↑ TG	↑ VLDL, ↓HDL
4	Hypothyroidism	↑ Chol	↑LDL
5	Obstructive liver disease	↑ Chol	↑LP(a)
6	Alcoholism	↑ TG	↑ VLDL
7	Oral contraceptive	↑ TG	↑ VLDL, ↓HDL
8	β- Adrenergic blocking agents	↑ TG	↑ VLDL, ↓HDL
9	Isotretinoin	↑ TG	↑ VLDL

Table No.4: Normal levels for lipid profile

S.No	Lipids	Desirable value (mg/dl)	Borderline (mg/dl)	High risk (mg/dl)
1	Cholesterol	Less than 200	200-239	240
2	Triglycerides	Less than 140	150-199	200-499
3	HDL cholesterol	60	40-50	Less than 40
4	LDL cholesterol	60-130	130-159	160-189
5	Cholesterol/HDL ratio	4.0	5.0	6.0

Table No.5: Existing hypolipidemic drugs

Class	Drugs	Major effect	Dose	Side effects
HMG CoA reductase inhibitor	Mevastatin	Lower LDL-C concentration	20-40mg/day orally	Depression, anxiety, indigestion
	Lovastatin	Same above	40mg/day orally	Headache, rashes, gastrointestinal symptoms
	Pravastatin	Same above	30mg/day orally	Depression, anxiety, alopecia
	Simvastatin	Same above	5-10mg/day orally	Memory loss
	Atorvastatin	Same above	10,20,40,80 /day orally	Sore throat, fever, skin rash, vomiting
Fibrates	Clofibrate	Lower serum TG concentration	2gm/day orally	Nausea, diarrhoea, arthralgias
	Gemfibrozil	Lower plasma TG concentration by 40-55%	1.2gm/day orally	Abdominal pain, nausea, diarrhoea
	Fenofibrate	Lower plasma LDL-C conc. and rise HDL-C concentration	2-5gm/day orally	Nausea, Constipation, skin rashes
	Ciprofibrate	Same as above	5gm/day orally	Constipation, skin rashes
	Bezafibrate	Suppresses endogenous cholesterol and TG synthesis	5gm/day orally	Myalgia, diarrhoea, skin rashes
	Simfibrate	Lower cholesterol concentration and TG concentration	1.5gm/day orally	Skin rashes, nausea, myalgia
	Etofibrate	Lower VLDL-C and LDL concentration	900mg/day orally	Flushing
Antioxidant	Probucol	Lower plasma cholesterol by 10-15%	250-500mg/day orally	Flatulence, eosinophilia, paresthesia
Other lipid-lowering drugs	Nicotinic acid	Lower LDL-C concentration	2-6gm/day orally	Vomiting, dyspepsia
	Neomycin	Same as above	0.5-2gm/day orally	Malabsorption, diarrhoea
	β- sitosterol	Same as above	6gm/day orally	The laxative effect, vomiting
	Dextro thyroxin	Lower plasma LDL-C concentration	1-2gm/day orally	Serious cardiac toxicity
	Aminosalicylic Acid	Same as above	2gm/day orally	Steatorrhea
	Tiadenol	Lower plasma Cholesterol level	1.6gm/day Orally	Nausea
	Sorbinicate	Lower Chol concentration and TG plasma level	800gm/day orally	Malabsorption
Bile acid binding resins	Cholestyramine	Binds bile acid resulting in Chol catabolism	12-16mg/day	Nausea, indigestion
	Colestipol	Lower plasma LDL-C levels	15-30mg/day orally	Nausea, constipation
Cholesterol absorption inhibitor	Ezetimibe	↓elevated TG, LDL-C, Apo B	10mg/day orally	Unusual muscle weakness, tenderness, nausea

Table No.6: Solubility parameters

S.No	Descriptive term	Parts of solvent required for part of solute
1	Very soluble	Less than 1
2	Freely soluble	From 1 to 10
3	Soluble	From 10 to 30
4	Sparingly soluble	From 30 to 100
5	Slightly soluble	From 100 to 1000
6	Very slightly soluble	From 1000 to 10000
7	Practically insoluble	From 10000 to more

Table No.7: Formulation of solid dispersion with PVP K30: HPMC E5

Formulation Code	Ratio	ATC (mg)	PVP K30 (mg)	HPMC E5 (mg)
F1	1:1:1	200	200	200
F2	1:2:1	200	400	200
F3	1:3:1	200	600	200
F4	1:4:1	200	800	200
F5	1:2:2	200	400	400
F6	1:1.5:1.5	200	300	300

Table No.8: Role of excipients

S.No	Excipients	Functional Category
1	Starch	Binder
2	Microcrystalline Cellulose	Diluent, Disintegrant, anti-adherent
3	Croscarmellose sodium	Disintegrant
4	Magnesium Stearate	Lubricant
5	Talc	Glidant

Table No.9: Formulation table for atorvastatin calcium tablets

S.No	Ingredients	For one tablet (mg)	For 100 tablets (g)
1	ATC solid dispersion	61.22	6.122
2	Starch	q.s	q.s
3	Microcrystalline Cellulose	78.28	7.828
4	Croscarmellose sodium	6	0.6
5	Magnesium Stearate	3	0.3
6	Talc	1.5	0.15

Table No.10: Official limits for weight variation test as per IP

S.No	Average weight of tablets (mg)	Maximum percentage difference allowed (%)
1	≤80	±10
2	80-250	±7.5
3	≥250	±5

Table No.11: Official limits for disintegration test as per IP

S.No	Type of tablets	IP Limit (minutes)
1	Uncoated tablets	15
2	Coated tablets	60
3	Enteric coated tablets	60
4	Film coated tablets	30
5	Effervescent tablet	5
6	Soluble tablet	3
7	Dispersible tablets	3

Table No.12: Standard graph of ATC

S.No	Concentration (µg/ml)	ATC Absorbance (246nm)
1	0	0
2	2	0.224
3	4	0.433
4	6	0.631
5	8	0.855
6	10	1.047

Table No.13: Solubility study in different solvents

S.No	Solvent	Amount of ATC (mg/ml)	Inference
1	Water	0.029	Practically insoluble
2	Phosphate buffer	0.074	Insoluble
3	0.1N HCI	0.008	Practically insoluble

Table No.14: FT-IR data of Atorvastatin calcium

S.No	Wavenumber cm^{-1}	Assignment
1	1652.09	Acid carboxylic C = O stretch
2	2968.55	C = H stretch
3	3255.95-3403.51	Inter molecular hydrogen bond, O-H stretch
4	Three peak 1436.05-1510.31	Aromatic C=C stretch
5	1240.27	C-F stretch
6	843.88	Ring Vibration due to para-substituted benzene
7	1436.05	C-N stretch
8	1510.31, 3364.93	N-H stretch

Table No.15: FT-IR data of Polyvinyl Pyrrolidone K30

S.No	Wavenumber CM^{-1}	Assignment
1	2956.01	C-H Asymmetric stretch
2	1651.12	C=0 Stretch
3	1291.39	C-N Stretch
4	3398.69	0-H Stretch
5	1423.51	CH_2 Bending

Table No 16: FT-IR data of Hydroxy Propyl Methyl Cellulose E5

S.No	Wavenumber CM-1	Assignment
1	1377.22	C-H Bending
2	1152.51	C-O Stretching
3	947.08	Secondary hydroxy

Table No.17: FT-IR data of Micro crystalline Cellulose

S.No	Wavenumber CM^{-1}	Assignment
1	1163.11	C-N Bending
2	1635.69	C-O Stretching
3	3339.86	0-H & N-H Stretching

Table No 18: FT-IR data of Croscarmellose Sodium

S.No	Wavenumber -1	Assignment
1	2851.85	C-H Stretch
2	1068.57	C-O Stretch
3	893.07	C-C Stretch
4	1023.31	C-O Stretch

Table No.19: FT-IR data of Magnesium Stearate

S.No	Wavenumber CM-1	Assignment
1	1113.93	C-CH3 Bending
2	1574.93	C-0 Stretching
3	2957.94	Symmetric C-H Stretching

Table No.20: FT-IR data of Talc

S.No	Wavenumber CM-1	Assignment
1	651.96	O-CH3 Stretching
2	1818.93	C-H Bending
3	2918.40	C-H Bending

Table No.21: FT-IR data of solid dispersion

S.No	Wavenumber CM-1	Assignment
1	1239.31	C-F Stretch
2	1534.42	N-H Stretch

Table No.22: Solubility study of prepared SDs

Formulation	ATC solubility study of prepared SDs
F1	0.245
F2	0.285
F3	0.311
F4	0.321
F5	0.285
F6	0.268

Table No.23: Weight variation test

Tablet	Weight in Mg	Tablet	Weight in Mg
1	150	14	150
2	149	15	149
3	150	16	152
4	150	17	148
5	149	18	150
6	150	19	150
7	150	20	149
8	148	Total weight	2995
9	151	Average weight	149.75
10	152	IP limit	±7.5%
11	150	Lower limit	138.51
12	150	Upper limit	160.98
13	148		

Table No.24: Hardness test

Tablet	Hardness Kg/cm2
1	5.2
2	5.3
3	4.9
4	4.6
5	4.7
6	4.9
IP LIMIT	4-6kg/cm2

Table No.25: Disintegration Test

Tablet	Disintegration Time (Minutes)
1	10
2	12
3	9
4	8
5	7
6	7
IP LIMIT	For uncoated tablet within 15 minutes

Table No.26: *In vitro* drug release of atorvastatin calcium from SD, Solid dispersion tablet and Marketed Product

Time (Mins)	Percentage drug release (%)		
	ATC Solid dispersion (F4)	ATC Solid dispersion tablet	Marketed Product
10	46.9	38.4	33.8
20	95.2	69.5	63.6
30	99.3	82.1	78.4
40	99.4	97.3	90.1
50	99	99	99
60	99	99	99

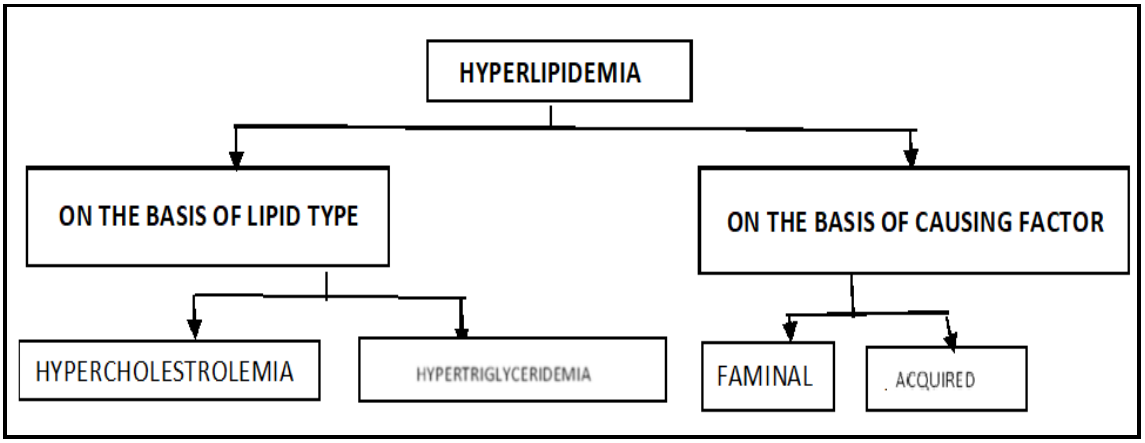


Figure No.1: Classification of hyperlipidemia

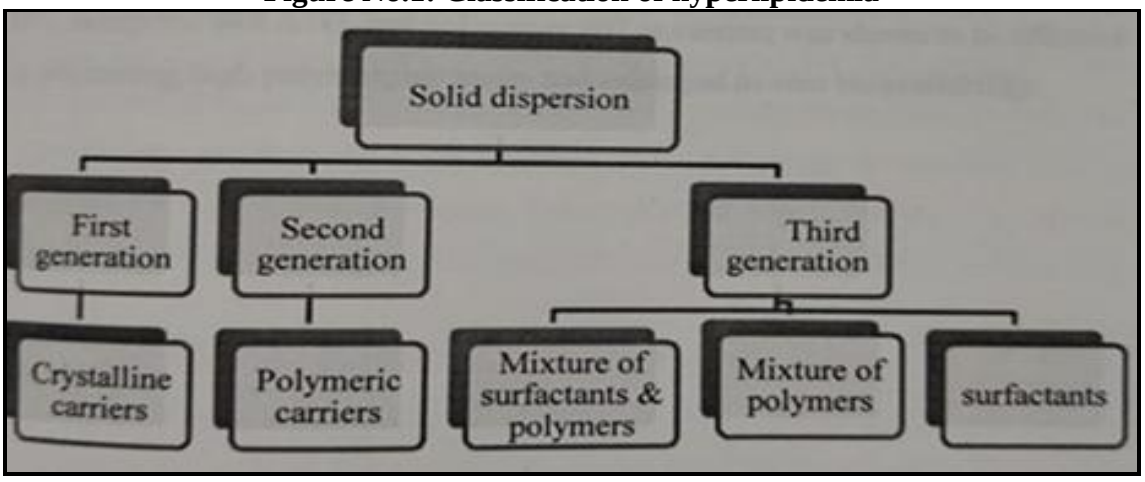


Figure No.2: Classification of SDs based on the carrier used

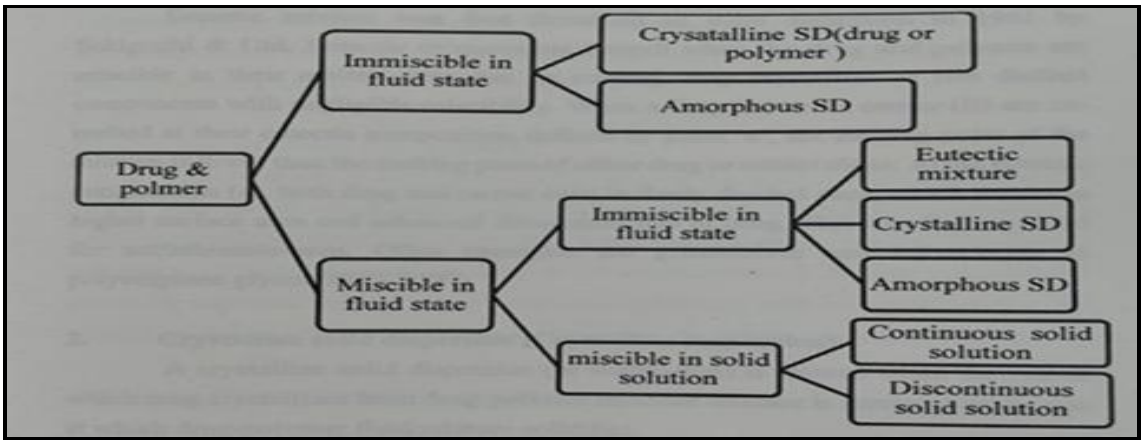
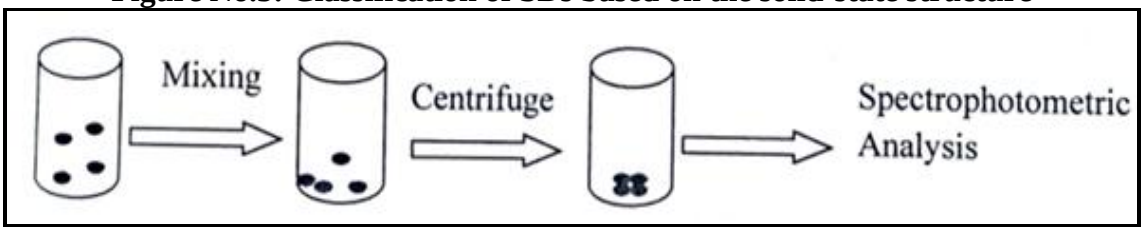


Figure No.3: Classification of SDs based on the solid-state structure



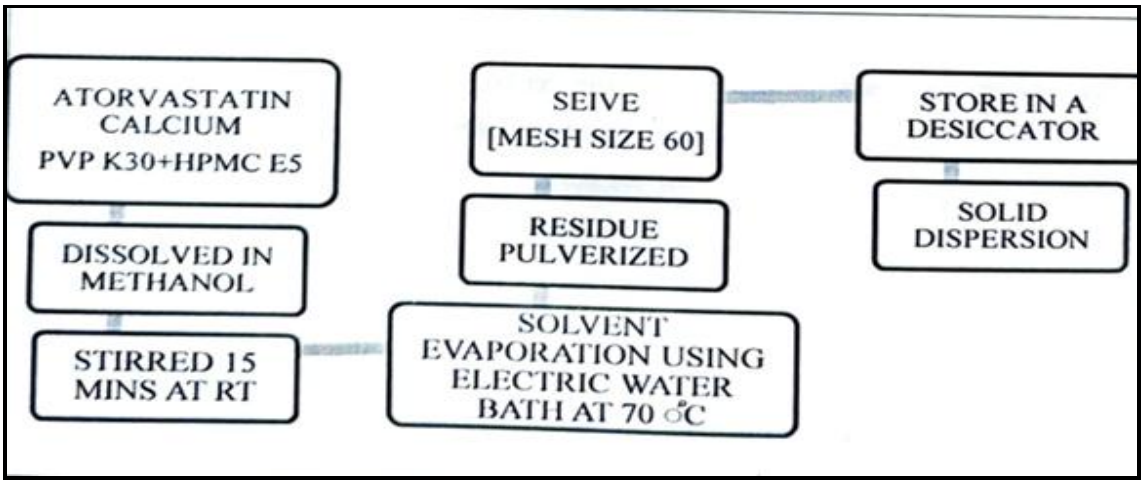


Figure No.4: Preparation of Solid dispersion

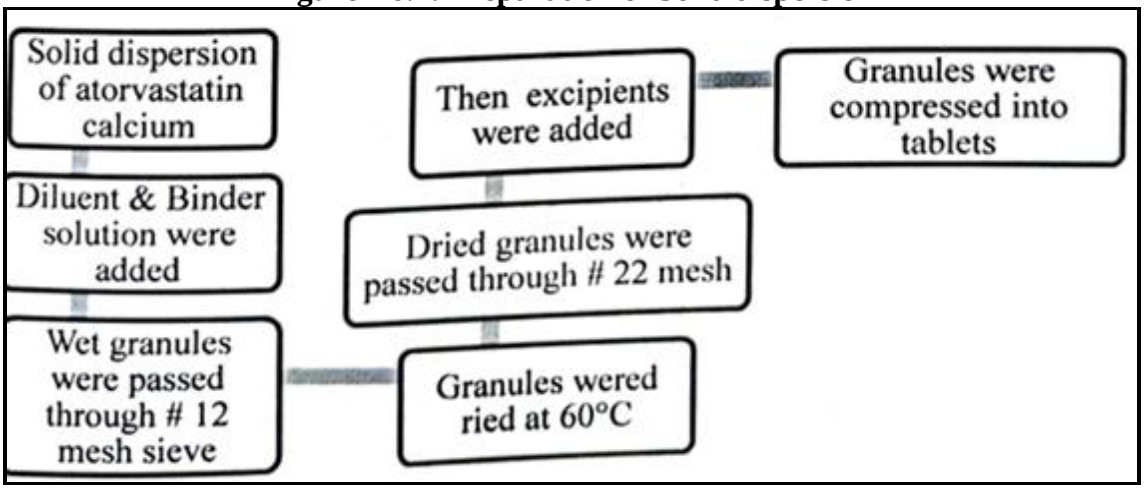


Figure No.5: Preparation of granules

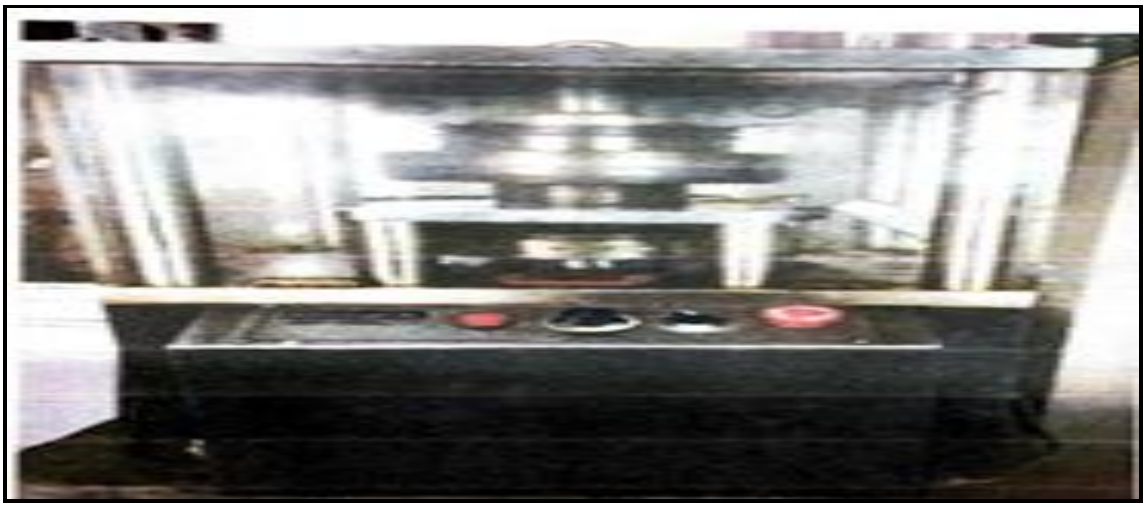


Figure No.6: Tablet punching machine

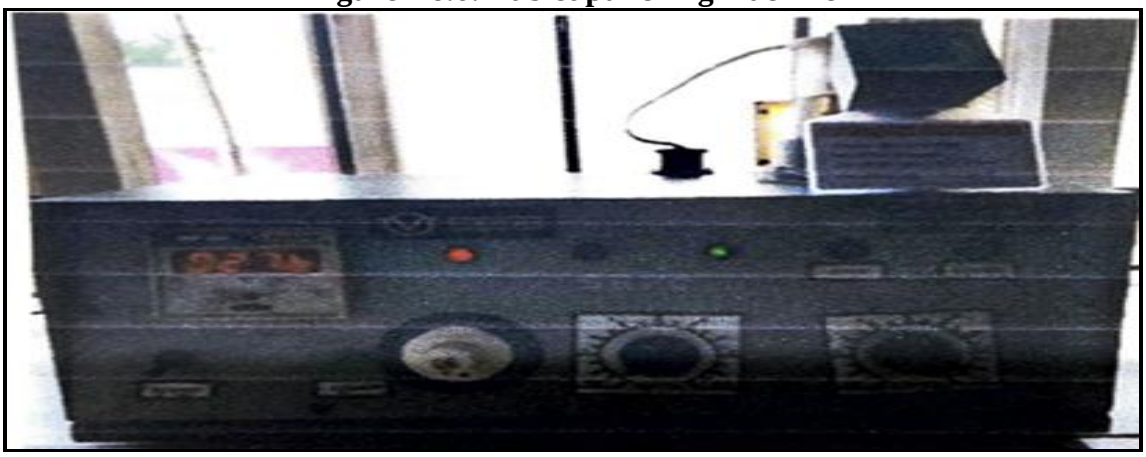


Figure No.7: Melting point detector

Figure No.8: λ max Atorvastatin Calcium

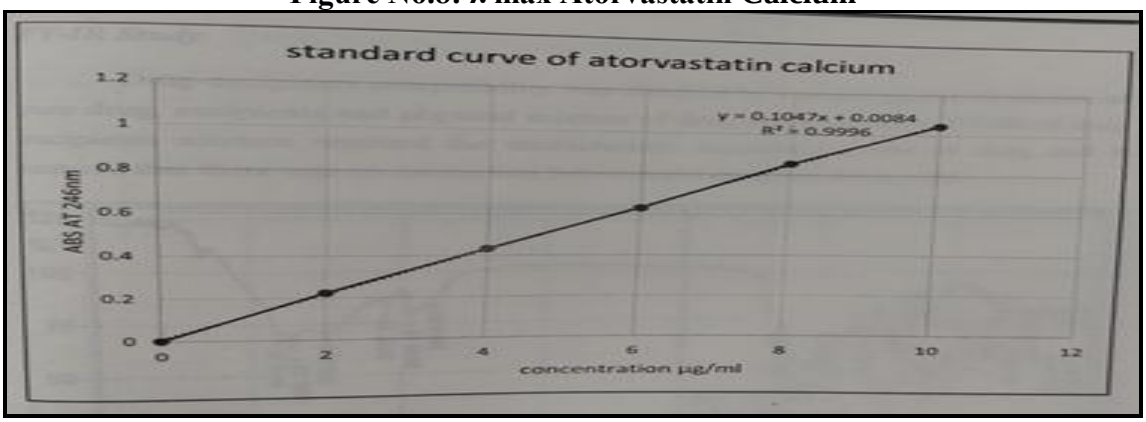


Figure No.9: Standard graph of ATC

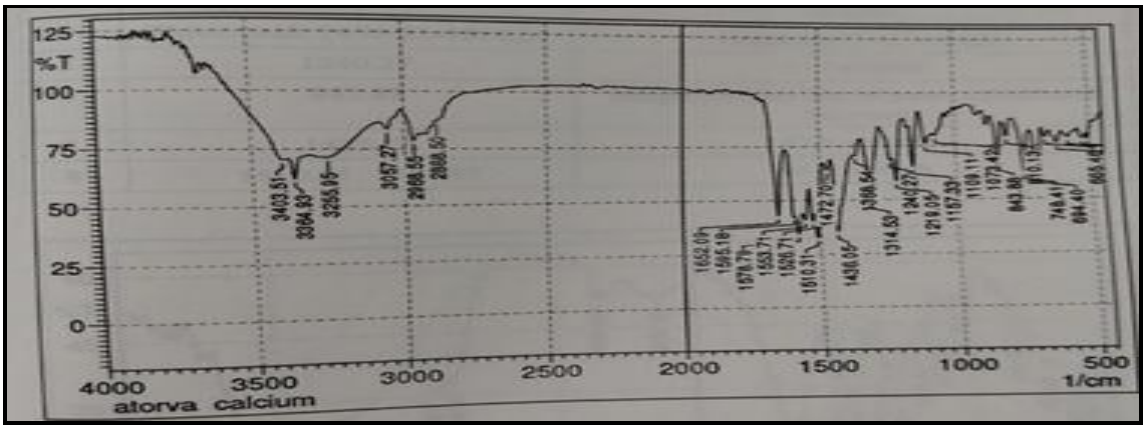


Figure No.10: FT-IR spectrum of Atorvastatin calcium

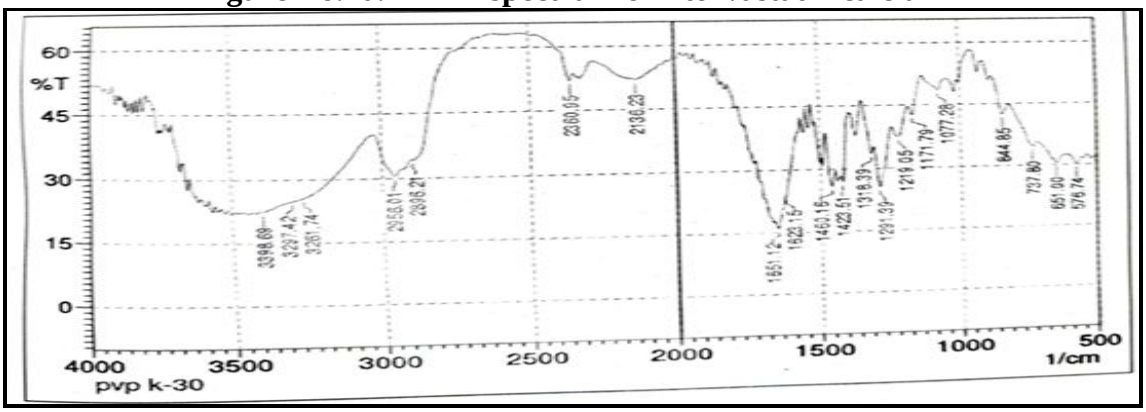


Figure No.11: FT-IR spectrum of Polyvinyl Pyrrolidone K30

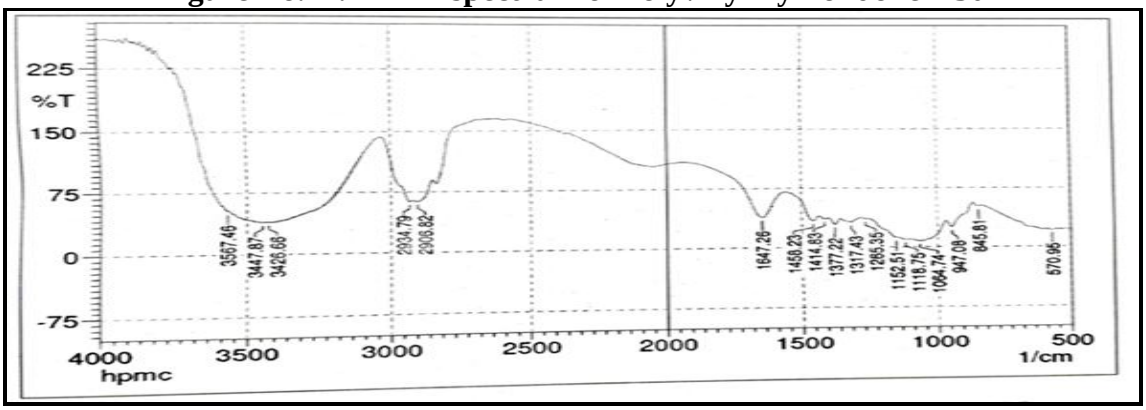


Figure No.12: FT-IR spectrum of IIydroxy Propyl Methyl Cellulose E5

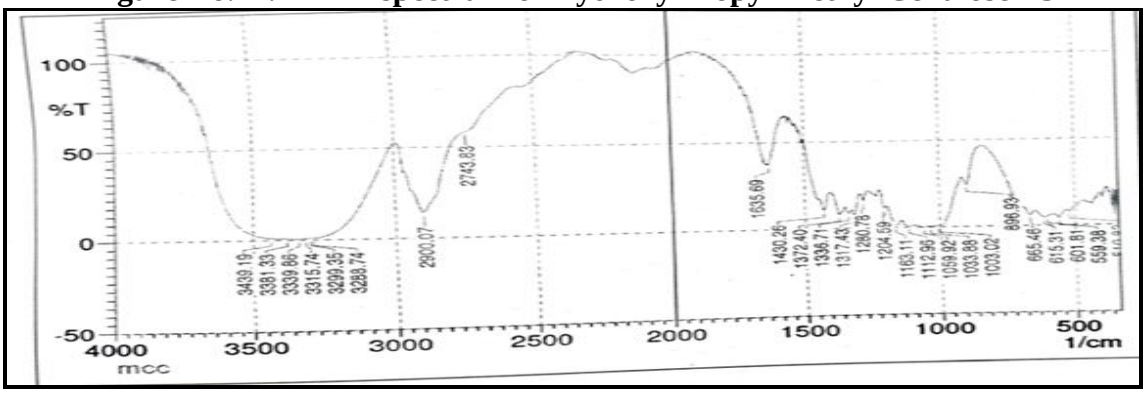


Figure No.13: FT-IR spectrum of Microcrystalline Cellulose

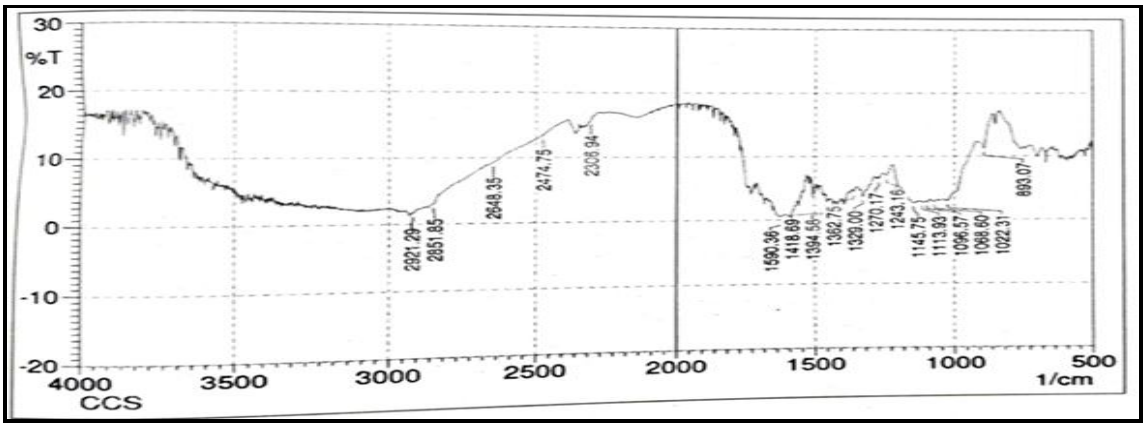


Figure No.14: FT-IR spectrum of Croscarmellose Sodium

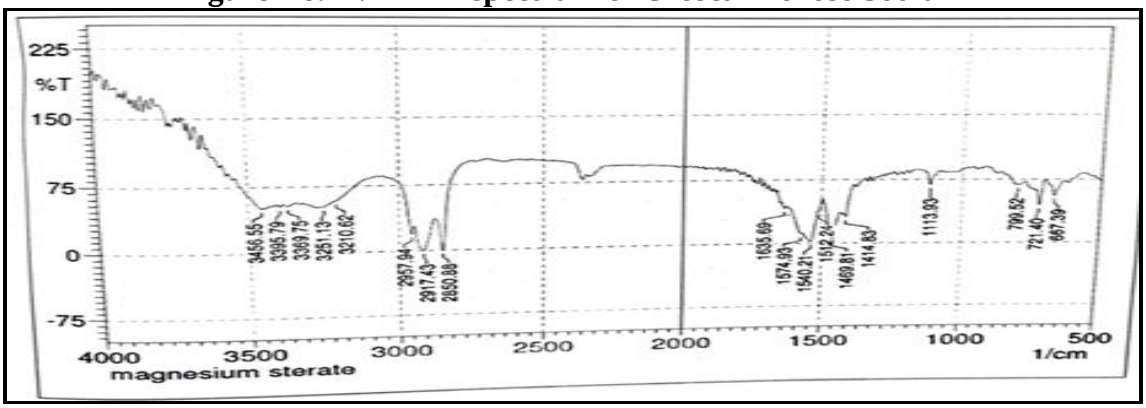


Figure No.15: FT-IR spectrum of Magnesium Stearate

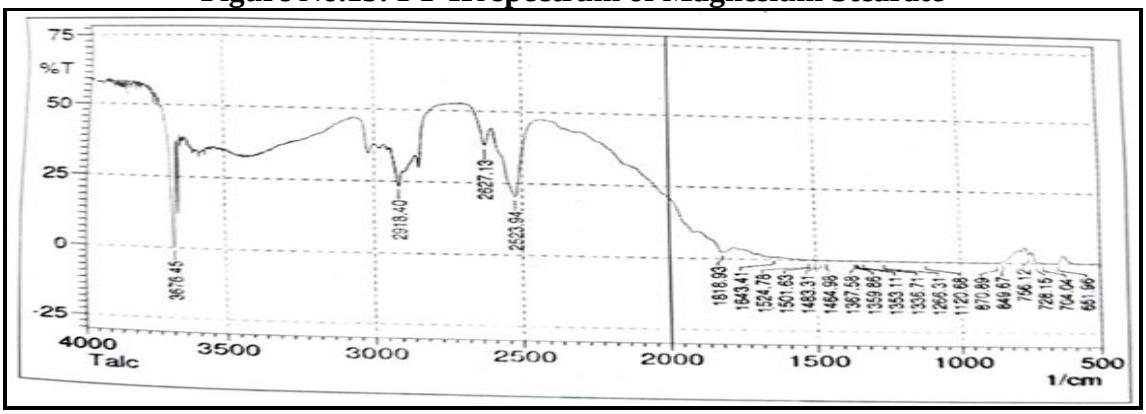


Figure No.16: FT-IR spectrum of Talc

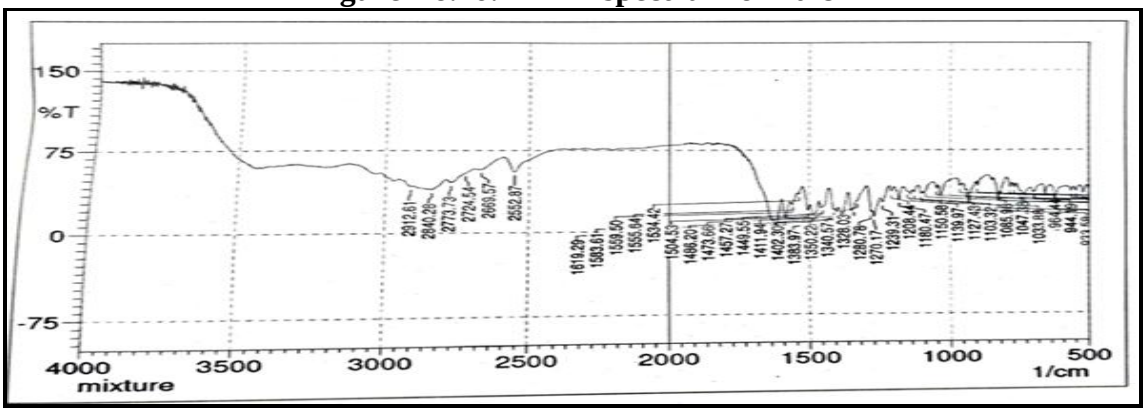


Figure No.17: FT-IR spectrum of solid dispersion (ATC: PVP K30: HPMC E5)

Figure No.18: Disintegration apparatus

Figure No.19: Labtronics dissolution apparatus

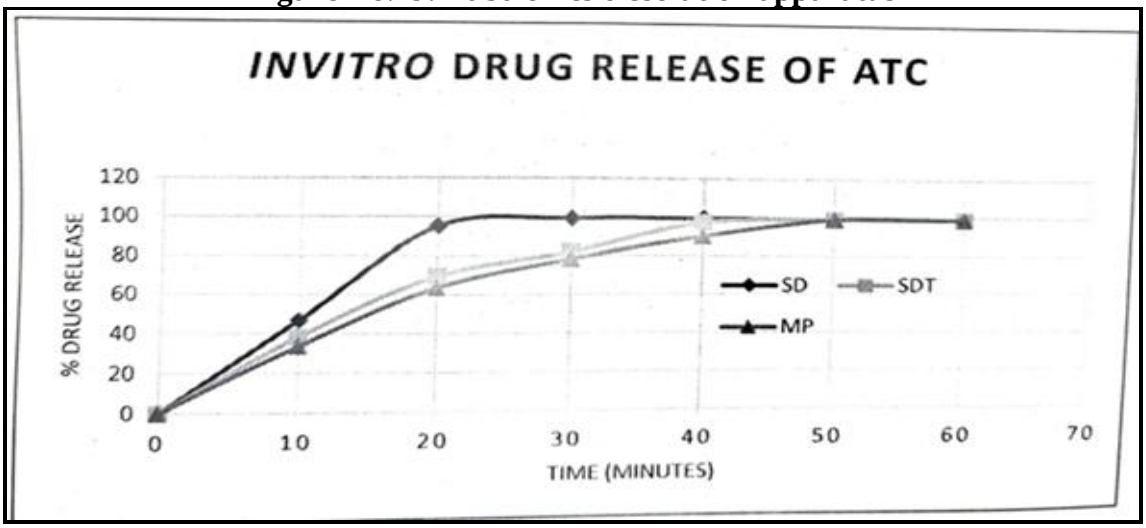


Figure No.20: *In vitro* drug release of atorvastatin from SD, solid dispersion tablet and marketed product

CONCLUSION

The present research work aimed to enhance the solubility of calcium by Atorvastatin solid dispersion. Solid dispersions were prepared by solvent evaporation method. Carriers such as PVP K30 and HPMC ES were used to prepare solid dispersion to improve the wettability of the particle and to reduce the interfacial tension between the drug particles. Various formulations were prepared by varying the concentration of carrier such as PVP K30: HPMC E5 (1:1, 2:1, 3:1. 4:1. 2:2. 1.5:1.5) to obtain an optimized formulation with suitable physical appearance. The prepared solid dispersions were subjected to solubility study, to select the best formulation.

The result showed that the formulation F4 containing 1:4:1 [ATC: PVP K30: HPMC ES) shows 12-fold increase in solubility when compared to pure drug. The optimized solid dispersion was formulated into tablet by wet granulation method. Compressed tablet was subjected to quality control test and it meets IP specifications. The *in vitro* dissolution study was performed using Phosphate buffer PH 6.8 dissolution media and it was compared with marketed product Lipvas®. The *in vitro* drug release study of tablet containing solid dispersion shows that 97.1% of ATC was released at 40minutes which was higher when compared to marketed product (90.3% ATC).

Overall results obtained during these work shows that solid dispersion could improve the dissolution rate of ATC, when using optimized carriers. It could be considered as a better choice for the treatment of hypercholesterolemia when converted into a suitable dosage form.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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