Solubility and Dissolution enhancement of Pitavastatin Calcium by using different polymers and formulated into tablet dosage form

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Abstract

Dyslipidemia and hypercholesterolemia are extremely common in general population and are regarded as a highly modifiable risk factor for cardiovascular diseases.
These are the two leading risk factors for heart diseases and causes an increase in coronary heart disease related events and more common in elderly patients.

Pitavastatin calcium is a BCS class II drug (low solubility and high permeability), used as a lipid lowering agent by inhibiting the endogenous production of cholesterol within the liver,it lower abnormal cholesterol and lipid levels and ultimately reduce the risk of cardiovascular disease . Pitavastatin competitively inhibit the enzyme HMG CoA reductase which catalyzes the conversion of HMG-CoA to mevalonic acid. it is used for the management and treatment of dyslipidemia and hypercholesterolemia.

BCS class 2 having low solubility & therefore low oral bioavailability. Solid dispersion of Pitavastatin calcium loaded with combination of HPMC and MC for the beneficial of cholesterol patients, to provide sustained release effect .The most challenging aspect for various new chemical entities is to increase in the solubility of poorly water soluble drug which leads to the unsatisfactory dissolution profile, consequently, the bioavailability. To improve dissolution rate, Solid dispersions in water-soluble carriers have attracted considerable interest to improve bioavailability of hydrophobic drug. The solid dispersions were prepared by kneading method using carriers at different drug carriers' ratio(HPMC and methylcellulose).

Key Words: Pitavastatin, Carriers, HPMC, MC, Solid Dispersions, Tablet.

Introduction

Solubility:

It is defined as the "concentration of a solute in a saturated solution at a certain temperature".The term 'solubility' is defined as maximum amount of solute that can be dissolved in a given amount of solvent. It can also be defined quantitatively as well as qualitatively. Quantitatively it is defined as the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms, solubility may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion

Table : Solubility Description chart

Conditions	Parts of Solvent required for Part of Solute
Very soluble	≤ 1
Freely soluble	1 to 10
Soluble	10 to 30
Sparingly soluble	30 to 100
Slightly soluble	100 to 1000
Very slightly soluble	1000 to 10,000
Practically insoluble, or soluble	10,000 or more

The process of solubilization involves the breaking of intermolecular or inter-ionic bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.

VARIOUS SOLUBILITY ENHANCEMENT TECHNIQUES

- **Solid dispersion**
- **Size reduction**
- **Liquid formulation**
- **Change in PH**
- **Surfactant**
- **Co-Solvency**
- **Inclusion complexes**
- **Salt formation**

DISSOLUTION:

Dissolution is defined as "the process by which a solid substance enters in solvent to yield a solution".The dissolution of a drug is important for its bioavailability and therapeutic effectiveness.

Table : Influence of some parameters on dissolution rate of drug

Parameters	Symbol	Influence on Drug Dissolution
Diffusion coefficient	D	Greater the value, faster the dissolution of drug. Diffusion decreases as the viscosity of dissolution medium increases.
Surface area of solid	A	Greater the surface area, faster the drug dissolution; can be micronisation of drug.
Water/oil partition coefficient	$K_{w/o}$	Higher the value, more the coefficient of drug and its hydrophilicity and faster the dissolution in aqueous fluids
Concentration gradient	(C_s-C_b)	Greater the concentration gradient, faster the diffusion and drug dissolution; can be increased by increasing drug solubility and the volume of dissolution medium.
Thickness of stagnant layer	H	More the thickness, lesser the diffusion layer and drug dissolution; can be decreased by increasing agitation.

BCS: BIOPHARMACEUTICAL CLASSIFICATION SYSTEM

The BCS is scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability.

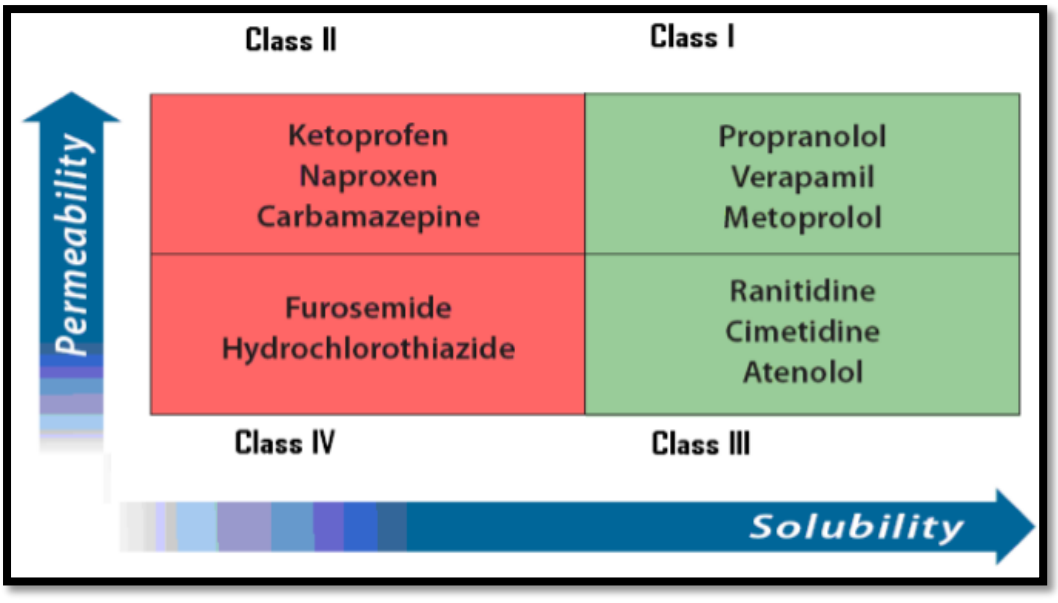

Table: Biopharmaceutical Classification System

Class	Solubility	Permeability	Characteristics features
I	High	High	well absorption orally
II	Low	High	variable absorption due to solubility limitation
III	High	Low	variable absorption due to permeability limitation
IV	Low	Low	poorly absorbed due to both solubility and permeability limitation

Material & Methods

Solid Dispersion

Solid dispersion refers to the dispersion of one or more active ingredients in a hydrophilic inert carrier matrix at molecular level.One of the underlying principles of formulation of solid dispersion is achievement of amorphous state which is considered to be more soluble than the crystalline state.Because in the amorphous state,no energy is required to break the crystal lattice found in the crystalline phase.

Types of Carriers used in Solid Dispersion

FIRST GENERATION (crystalline carrier)	SECOND GENERATION (polymeric carrier)	THIRD GENERATION (surfactants)
E.g. Urea, Sugars, Organic acids.	E.g. PVP, PEG, HPMC, Cyclodextrin.	E.g. Polaxomer, Tween 80, Gelucier44/141.

Ideal properties of carrier

- ✓ It should be readily soluble in water.
- ✓ Non-toxic and physiologically inert.
- ✓ High molecular weight.
- ✓ Melting point should be nearer to drug.
- ✓ High glass transition point – improve stability.

ADVANTAGES OF SOLID DISPERSION

1. Wetability is improved during solid dispersion production. Improved wetability results in increased solubility.
2. Preparation of solid dispersions results in particles with reduced particle size and thus the surface area is improved and increased dissolution rate is attained. The ultimate result is improved bioavailability.
3. To mask the taste of bitter tasting drugs.
4 To improve dissolvability in water of a poorly water-soluble drug in a pharmaceutical.
5. To prepare rapid disintegration oral tablets.
6. To obtain a homogenous distribution of small amount of drugs at solid state

7. To formulate a faster release priming dose in a sustained release dosage form.
8. To formulate sustained release dosage or prolonged release regimens of soluble drugs using poorly soluble or insoluble carriers.
9. Transformation of liquid form of drug into solid form.
10. Minimization of polymorphic changes and thereby bioavailability problems

Materials:

Drug: Pitavastatin Calcium

Polymers: HPMC, Methyl cellulose

Pitavastatin, also known as the brand name product Livalo, is a lipid-lowering drug belonging to the statin class of medications. By inhibiting the endogenous production of cholesterol within the liver, statins lower abnormal cholesterol and lipid levels and ultimately reduce the risk of cardiovascular disease. More specifically, statin medications competitively inhibit the enzyme hydroxymethylglutaryl-coenzyme A (HMG-CoA) Reductase,3 which catalyzes the conversion of HMG-CoA to mevalonic acid. Pitavastatin is an HMG-CoA reductase inhibitor used to lower lipid levels and reduce the risk of cardiovascular disease including myocardial infarction and stroke. It has beneficial effects on glucose control. As a consequence, pitavastatin is likely to be appropriate for patients with metabolic syndrome plus high LDL, low HDL and diabetes mellitus. Common side effects include headaches,nausea, abnormal liver function tests and muscle cramps.

Pitavastatin peak plasma concentrations are achieved about 1 hour after oral administration. The absolute bioavailability of pitavastatin is 51%. Pitavastatin has a relatively high bioavailability,which occurs due to enterohepatic reabsorption in the intestine following intestinal absorption. Pitavastatin is marginally metabolized by CYP2C9 and to a lesser extent by CYP2C8. It is excreted in feces (79%) and 15% in urine. The elimination half life is approximately 12 hours.

PREPARATION OF SOLID DISPERSIONS OF PITAVASTATIN

Kneading method

1) HPMC and Methyl cellulose are weighed ,they are mixed together in mortar pestle.
2) Water is added to mixture and mixture is converted to paste.
3) Pitavastatin is then added to the mixture and kneaded thoroughly.
4) The kneaded mixture is then dried in hot air oven for 2 hours at 50 C.
5) Then the solid dispersion passed to sieve no:60 to obtained uniform particle size.

Results & Discussion:

1. Physical appearance and Melting point

Physical appearance of drug was studied by its various organoleptic properties. The sample of Pitavastatin was found to be white, non-hygroscopic, crystalline solid powder.The melting point of Pitavastatin was found to be in the range of 135 -140^{0}C by Capillary method [40.

2.Differential scanning calorimetry

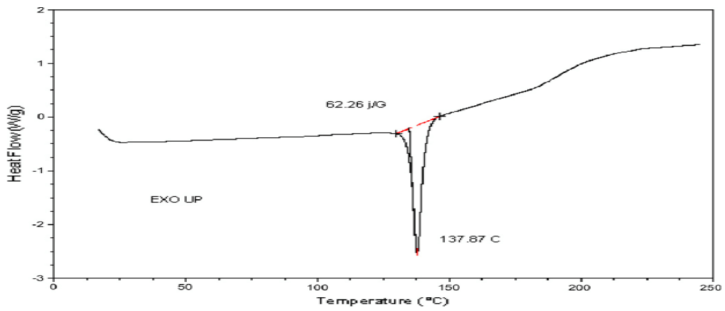

Figure : DSC thermogram of Pitavastatin

The DSC of the drug sample Pitavastatin shows a sharp endothermic peak at 137.87ºC that supports the purity and authenticity of the sample as shown in given Figure.

Solubility

The solubility studies of Pitavastatin were determined in different solvents.

Solubility of Pitavastatin in different solvents

Solvent	Solubility
Phosphate buffer	4.038±0.546
Water	1.688±0.358
0.1N HCL	2.168±0.628
Methanol	2.518±0.166

Data Expressed as mean ± S.D (n=3)

Drug Excipient Compatibility Studies

Physical mixtures of both Pitavastatin and excipients HPMC and Methyl Cellulose are prepared and put in to stability chamber for one month. No major changes were observed in the drug like there was no discoloration of the drug, No liquefaction between drug and polymer, No odour changes in the pure form of the drug was noticed which confirms the compatibility between the drug and excipients. The FTIR spectra of Pitavastatin and HPMC /MC physical mixtures are shown below which indicate that Pitavastatin compatible with the HPMC and Methyl Cellulose.

Table: Drug Excipient compatibility study between PIT/HPMC

	Week 1	**Week 2**	**Week3**	**Week 4**
Drug				3558cm^{-1},3012cm^{-1},1268 cm^{-1} 1164cm^{-1},2870cm^{-1}
Drug +polymer				3468cm^{-1},2938cm^{-1},1712 cm^{-1} 1648cm1462cm^{-1}

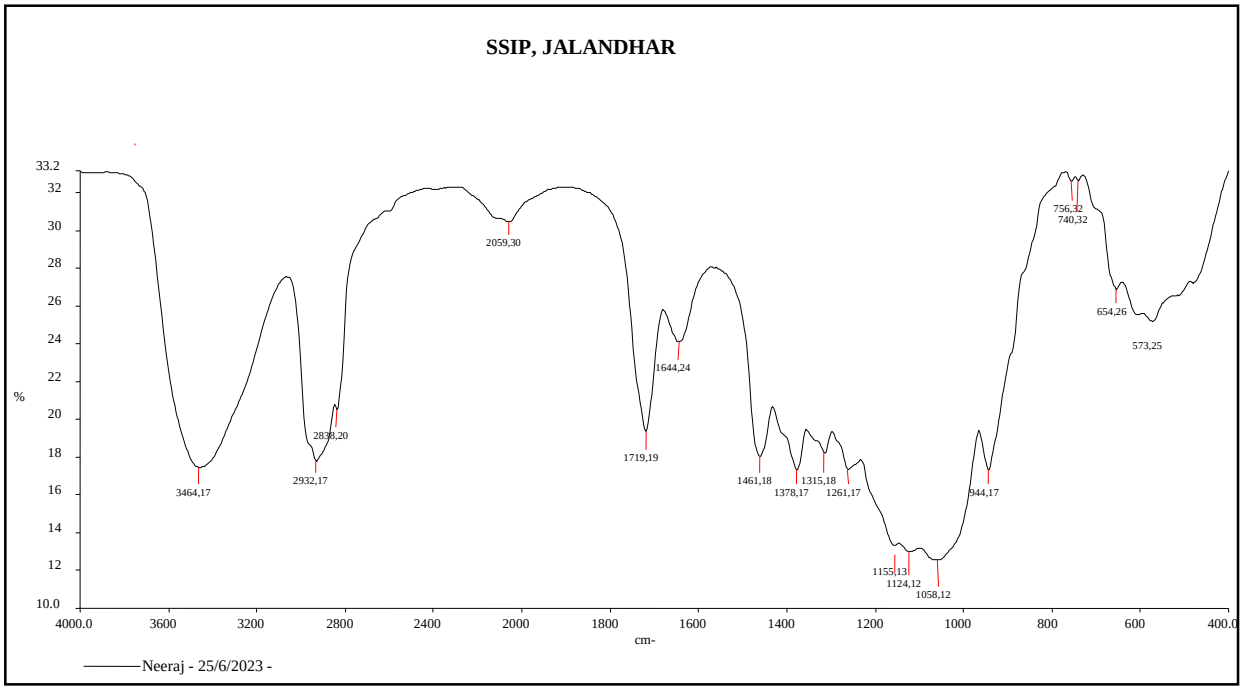

Figure : IR Spectra of Mixture of Drug & HPMC

Table : Drug Excipient compatibility study between PIT/MC

	Week 1	**Week 2**	**Week3**	**Week 4**
Drug				3558cm^{-1},3012cm^{-1} 1268 cm^{-1}1162cm^{-}2878cm^{-1}
Drug +polymer				3836cm^{-1},3446cm^{-1}, 2932cm^{-1},2058cm^{-1}

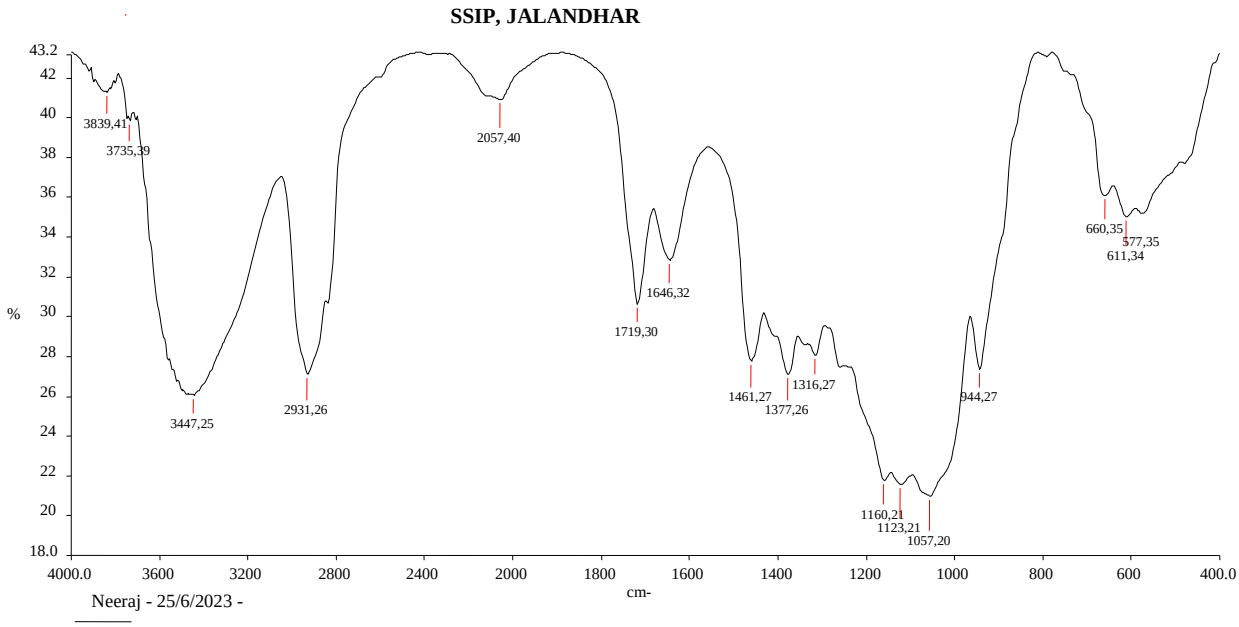

Figure: IR Spectra of Mixture of Drug & MC

Standard curves

The standard curve of Pitavastatin was found to be linear at 238 nm in phosphate buffer (pH6.8) in the concentration range of 2-12(µg/ml), which obeys Lambert Beer Law. The absorbance at different concentrations is shown in tables and graph is represented in figure respectively.

Table : Standard Curve of Pitavastatin in Phosphate Buffer (pH6.8)

S No.	Concentration(µg/ml)	Absorbance
1	2	0.135±0.024
2	4	0.237±0.008
3	6	0.344±0.014
4	8	0.464±0.034
5	10	0.556±0.033
6	12	0.662±0.033

Data Expressed as mean ± S.D (n=3)

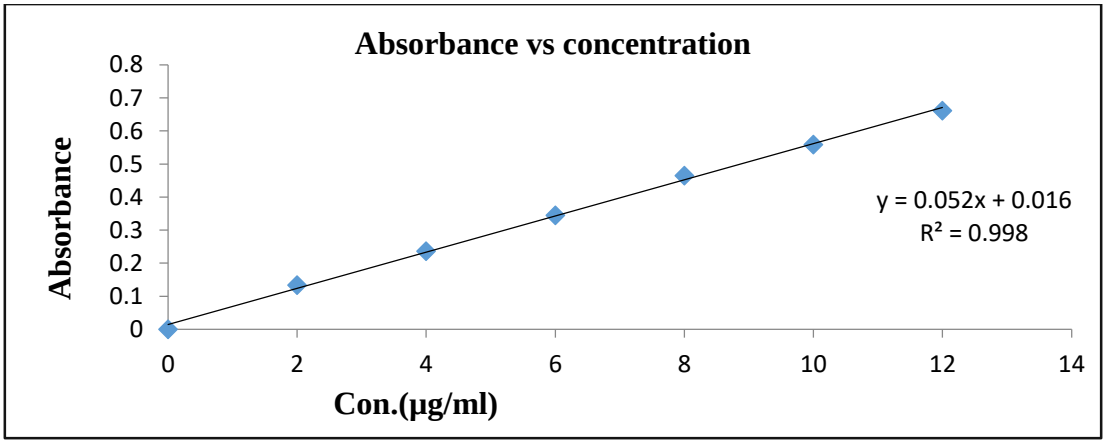

Fig.: Standard Curve of Pitavastatin in Phosphate Buffer (pH6.8)

Table : Standard Curve of Pitavastatin in distilled water

S No.	Concentration(µg/ml)	Absorbance
1	2	0.146±0.028
2	4	0.246±0.038
3	6	0.362±0.038
4	8	0.462±0.018
5	10	0.552±0.038
6	12	0.678±0.022

Data Expressed as mean ± S.D (n=3)

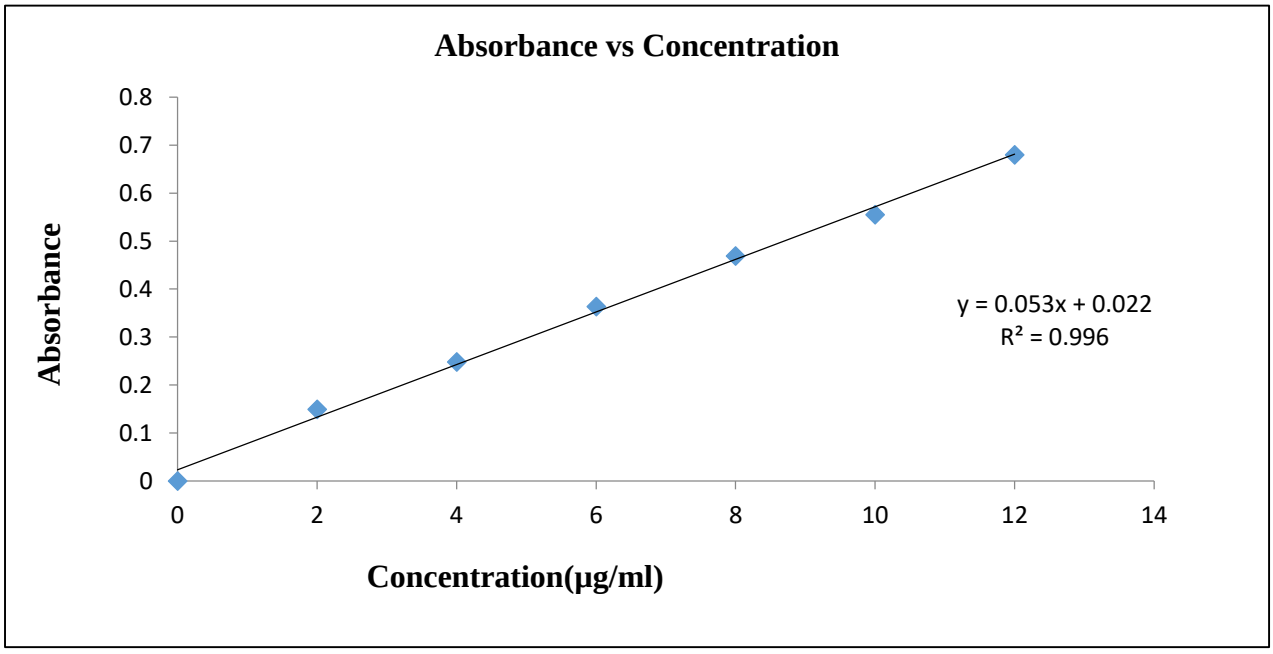

Fig.: Standard Curve of Pitavastatin in Distilled water

Table : Standard Curve of Pitavastatin in Methanol

S No.	Concentration(µg/ml)	Absorbance
1	2	0.126±0.016
2	4	0.244±0.016
3	6	0.346±0.014
4	8	0.434±0.018
5	10	0.536±0.024
6	12	0.648±0.024

Data Expressed as mean ± S.D (n=3)

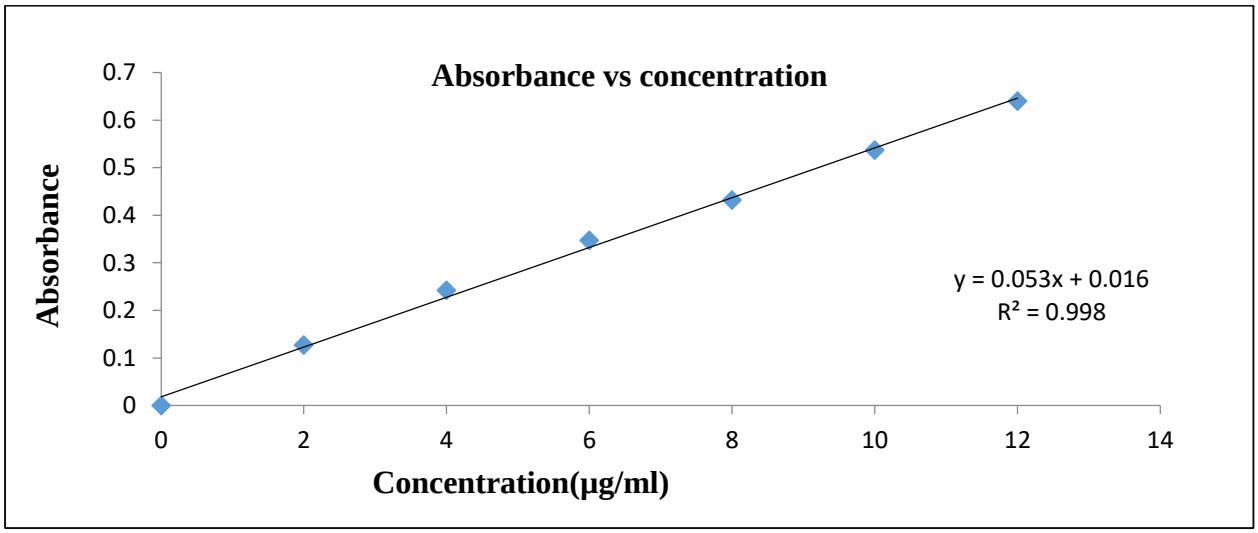

Fig.: Standard Curve of Pitavastatin in Methanol

Table : Standard Curve of Pitavastatin in 0.1NHCL

S No.	Concentration(µg/ml)	Absorbance
1	2	0.124±0.018
2	4	0.258±0.046
3	6	0.368±0.026
4	8	0.472±0.026
5	10	0.558±0.023
6	12	0.652±0.028

Data Expressed as mean ± S.D (n=3)

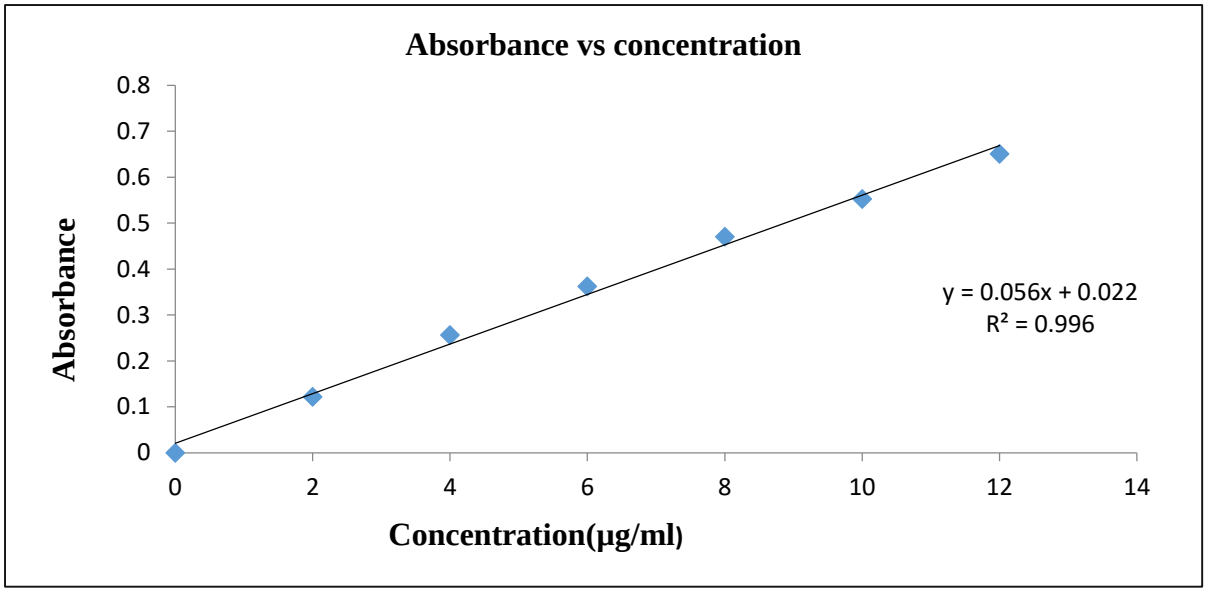

Fig.: Standard Curve of Pitavastatin in 0.1 HCL

Percent yield and drug content

The percent yield and drug content of pure drug and different solid dispersions which are prepared with polymers were determined. The % yields decreased at the higher concentrations due to the difficulty in sieving at higher polymer and surfactants concentration.

Table :Percent yield or drug content of solid dispersions Pit/HPMC

Formulation Code	Percentage yield	Drug content
PIH1:1	95.56±0.802	84.46±0.024
PIH1:3	94.86±0.634	91.78±0.018
PIH1:5	90.22±0.244	95.99±0.018

Data Expressed as mean ± S.D (n=3)

Table : Percent yield or drug content of solid dispersions Pit/MC

Formulation Code	Percentage yield	Drug content
PT1:1	90.16±0.756	78.68±0.018
PT1:3	89.66±0.514	88.88±0.014
PT1:5	89.24±0.864	83.24±0.016

Data Expressed as mean ± S.D (n=3)

Table : Percentage yield and drug content of solid dispersion Pitavastatin MC: HPMC

Formulation Code	Percentage yield	Drug content
PTM1:1	94.28±0.938	86.78±0.018
PTM1:3	92.99±0.408	88.62±0.016
PTM1:5	94.56±0.408	94.12±0.016

Data Expressed as mean ± S.D (n=3)

Solubility studies

Solubility data of pure drug and different solid dispersions as shown in given Tables respectively. Solubility of drug increased with increased in the ratio of polymer.

Table: Solubility of Pure Drug Pitavastatin and HPMC

Formulation Code	Solubility
Pure drug	4.138±0.546
PTH 1	6.156±0.644
PTH2	7.048±0.422
PTH3	8.274±0.154

Data Expressed as mean ± S.D (n=3)

Table: Solubility of Pure Drug Pitavastatin and MC

Formulation Code	Solubility
Pure drug	4.138±0.548
PT1	5.356±0.284
PT2	6.168±0.354
PT3	7.678±0.442

Data Expressed as mean ± S.D (n=3)

Table: Solubility of Pure Drug Pitavastatin and HPMC: MC

Formulation Code	Solubility
Pure drug	4.138±0.548
PTM1	9.516±0.236
PTM2	11.186±0.178
PTM3	12.516±0.232

Data Expressed as mean ± S.D (n=3)

Dissolution studies

The In vitro release of pure drug and different solid dispersions were determined and plotted the graph between % drug released vs time.

Table: Dissolution profile of pure drug and solid dispersions Pit/HPMC

Mean Percentage Drug Release ± Standard deviation				
Time (min)	**Pure drug**	**PT1:1**	**PT1:3**	**PT1:5**
10	8.428± 2.648	28.56±0.408	38.18±0.054	56.18±0.454
20	20.18±2.606	35.52±0.218	49.78±0.018	68.54±0.412
30	21.58±0.114	38.84±0.218	53.88±0.578	72.22±0.574
40	22.33±0.028	40.52±0.056	57.54±0.618	75.28±0.564
50	22.74±0.276	45.06 ± 0.036	61.36±0.546	82.68±0.684
60	25.16±0.146	46.26 ± 0.066	65.84±0.156	83.46±0.328

Data Expressed as mean ± S.D (n=3)

Fig: In vitro dissolution profile of %drug released vs time pure drug and Solid dispersions (Pit/HPMC)

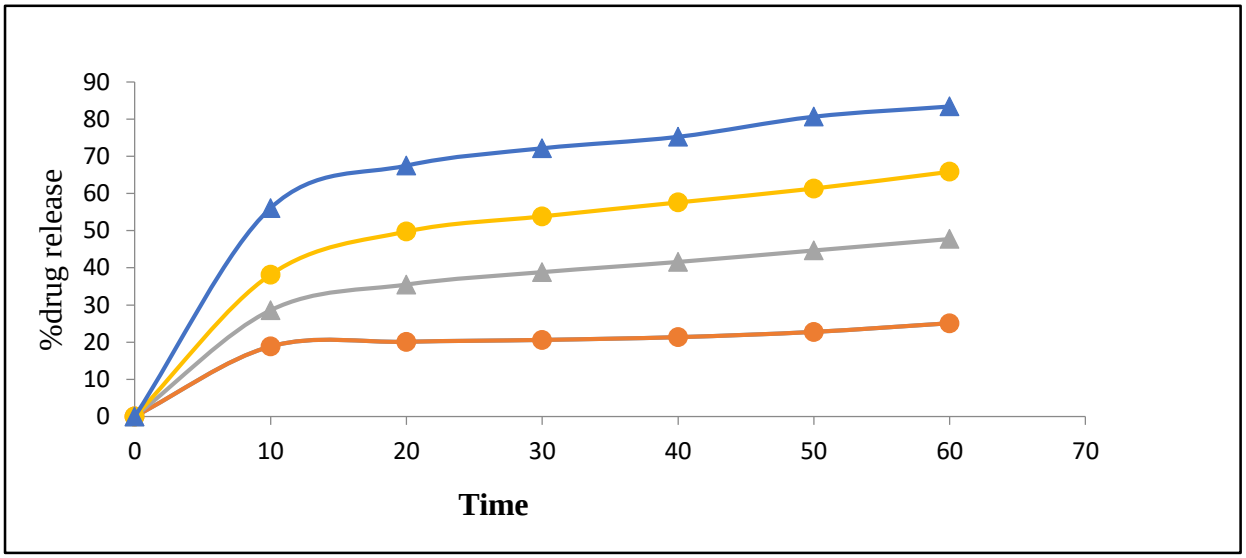

Table: Dissolution efficiency of pure drug or solid dispersion PIT/HPMC

Formulation code	D.E(%DE_{60})
Pure drug	19.96±0.008
PIH 1:1	35.66±0.998
PIH 1:3	50.18±1.956
PIH 1:5	65.48±1.908

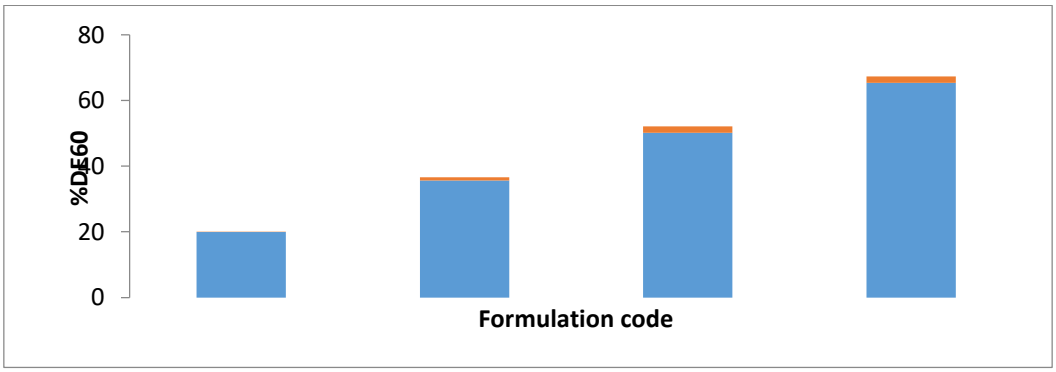

Fig.: Comparison of %DE60 of pure drug and different formulations with HPMC

Table: Dissolution profile of pure drug and solid dispersions PIT/MC

Mean Percentage Drug Release ± Standard deviation				
Time (min)	**Pure drug**	**PT1:1**	**PT1:3**	**PT1:5**
10	8.418± 2.644	32.42±0.406	43.76±0.434	48.08±0.354
20	20.08±2.604	37.68±0.132	45.26±0.458	53.42±0.224
30	20.56±0.016	39.18±0.132	47.18±0.474	57.92±0.434
40	21.36±0.028	41.68±0.236	51.36±0.182	60.17±0.92
50	22.76±0.276	45.06 ± 0.142	56.44±0.458	60.58±0.118
60	25.08±0.146	47.84 ± 0.262	59.58±0.066	70.59±0.302

Data Expressed as mean ± S.D (n=3)

Fig: In vitro dissolution profile of %drug released vs time pure drug and Solid dispersions (Pit/MC)

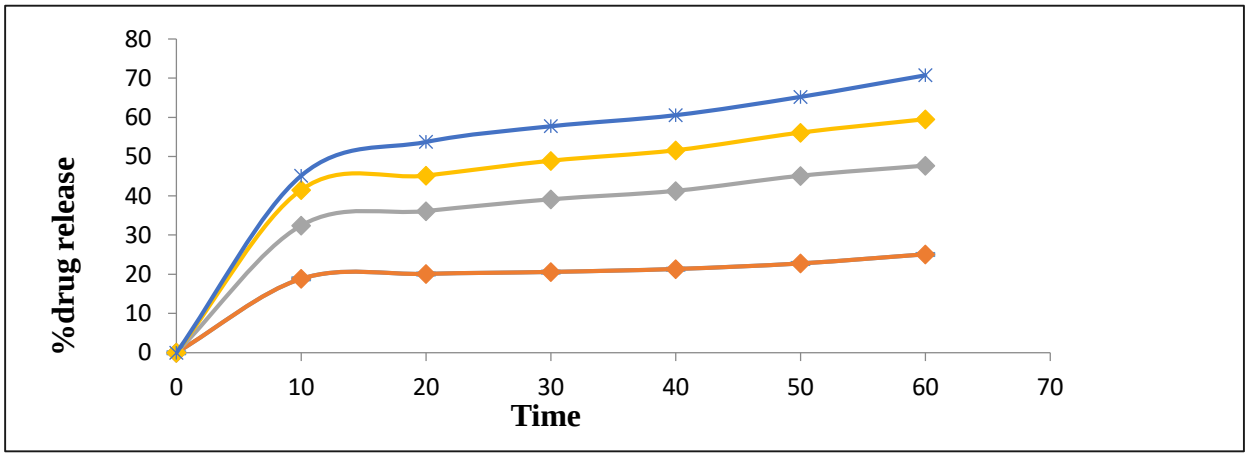

Table: Dissolution efficiency of pure drug or solid dispersion PT/MC

Formulation code	D.E(%DE_{60})
Pure drug	18.98±0.018
PTM 1:1	36.68±0.228
PTM 1:3	46.66±0.218
PTM 1:5	54.43±1.548

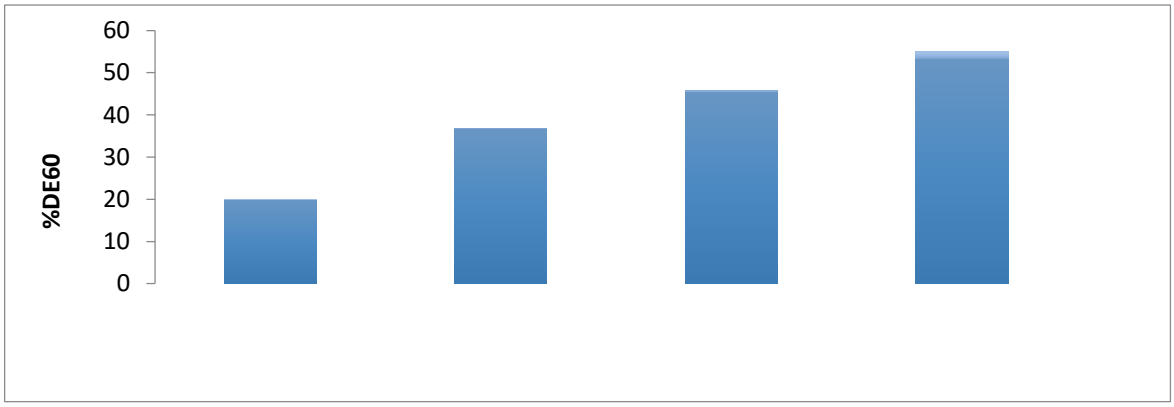

Fig.: Comparison of %DE60 of pure drug and different formulations with MC

Table: Dissolution profile of pure drug and solid dispersions MC: HPMC

Mean Percentage Drug Release ± Standard deviation				
Time (min)	**Pure drug**	**PT1:1**	**PT1:3**	**PT1:5**
10	8.412± 2.648	43.36±0.134	47.18±0.278	48.56±0.196
20	20.18±2.616	48.78±0.094	48.94±0.228	52.32±0.186
30	20.68±0.026	55.56±0.326	52.26±0.248	62.36±0.134
40	22.64±0.028	59.94±0.246	61.58±0.234	74.28±0.304
50	22.78±0.276	62.56 ± 0.036	73.18±0.176	82.18±0.058
60	25.18±0.148	69.86 ± 0.188	80.22 ±0.174	94.52 ±0.344

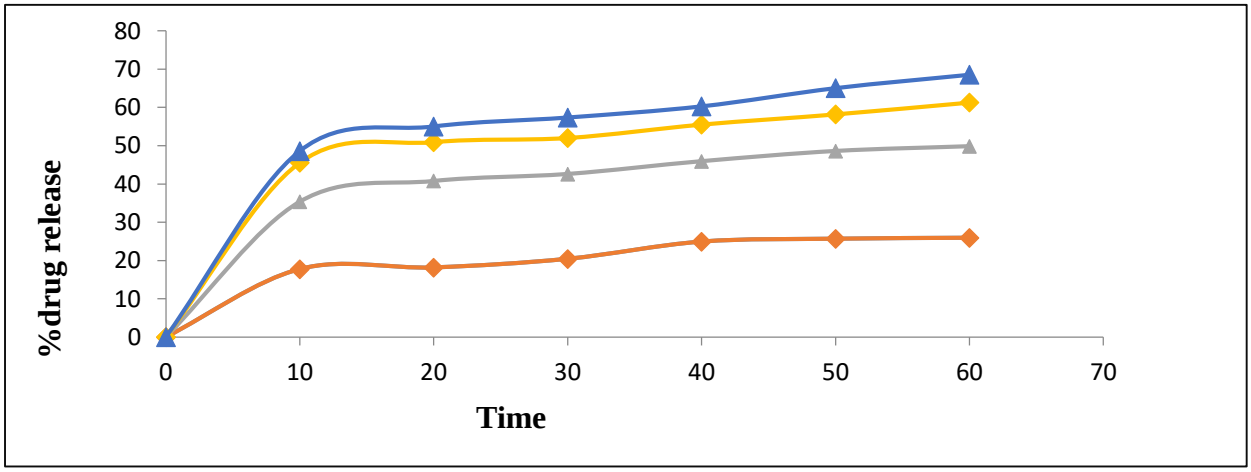

Fig: In vitro dissolution profile of %drug released vs time pure drug and Solid dispersions (Pit/MC: HPMC)Table: Dissolution efficiency of pure drug or solid dispersion HPMC/MC

Formulation code	D.E(%DE_{60})
Pure drug	18.98±0.016
PTV 1:1	52.84±0.194
PTV 1:3	54.82±0.464
PTV 1:5	62.94±0.066

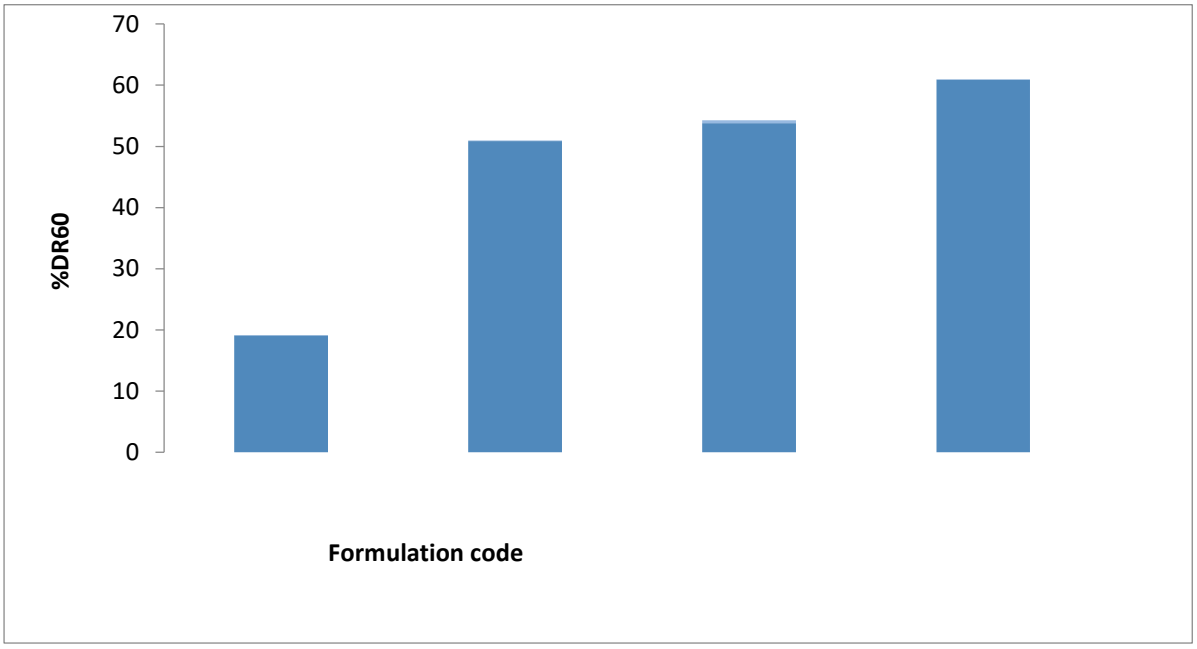

Fig.: Comparison of %DE60 of pure drug and different formulations with HPMC: MC

Infrared spectroscopy

Spectra of Pitavastatin and optimized solid dispersions of combination of HPMC and Methyl cellulose. The spectrum of solid dispersions exhibited significant decrease in intensity of O-H stretching vibrations which may be due to intermolecular hydrogen bonding. The spectra peaks of drug were almost unchanged in the optimized solid dispersions which indicate that the overall symmetry of molecule was not affected

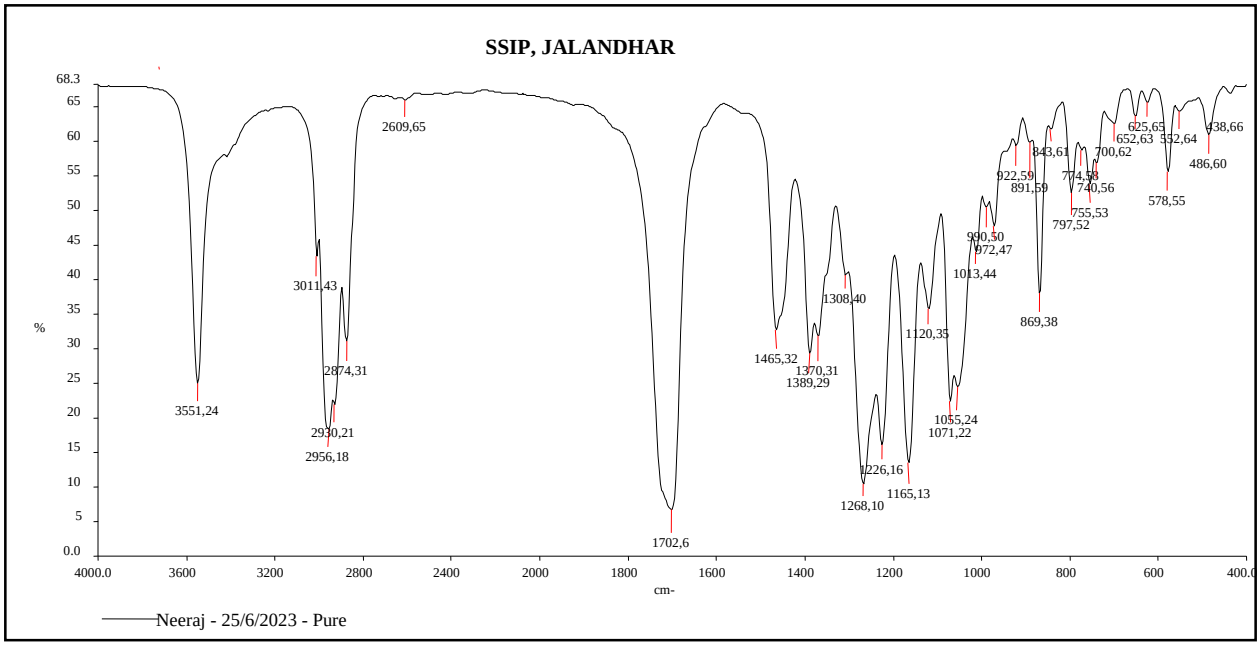

Figure: IR Spectra of Pitavastatin

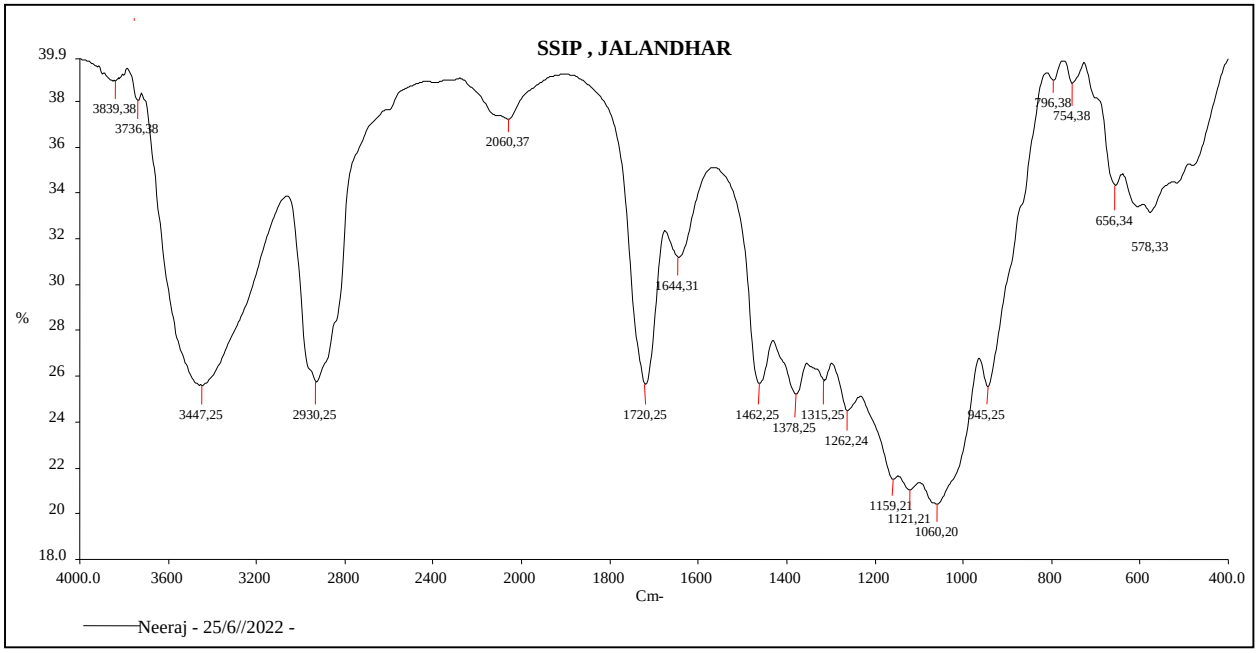

Figure: IR Spectra of optimized solid dispersion with (HPMC/MC)

X-ray diffraction studies

The X-ray diffraction studies of pure Pitavastatin and optimized solid dispersions of both polymers HPMC and Methyl Cellulose.The characteristics diffraction peaks of Pitavastatin present peaks at (2θ) 9.64º, 11.26º, 15.92º, 16.88º, 17.54º, 18.14º, 19.76º, 22.82º, 28.66º, 33.52º, 35.18º, and 38.76º indicate the pr crystalline nature of the drug. Peaks of optimized solid dispersion shows the reduction in peak height area which indicates the reduction in the crystallinity nature of the Pitavastatin as some of the drug converted into the amorphous form in the solid dispersions.

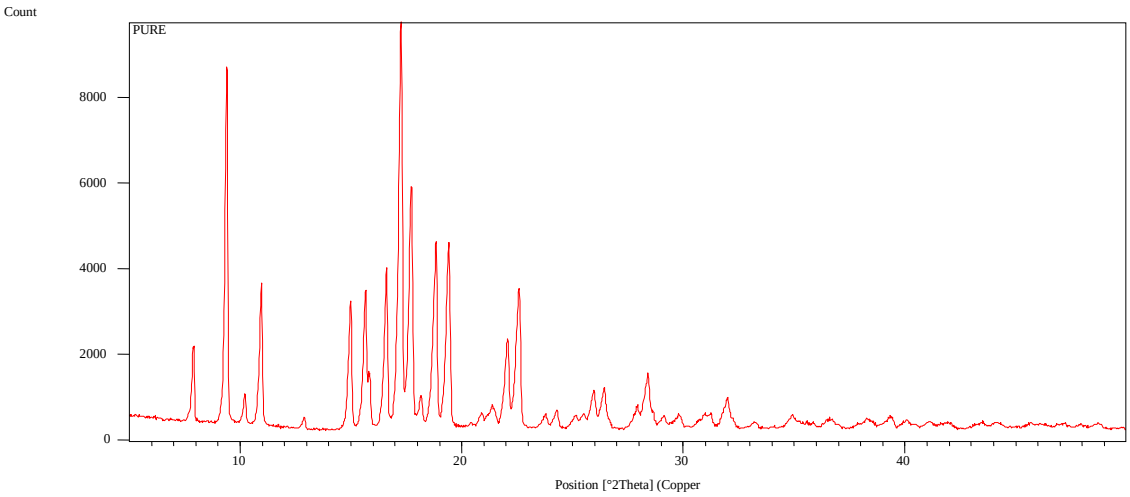

Fig. X-ray diffraction of Pitavastatin

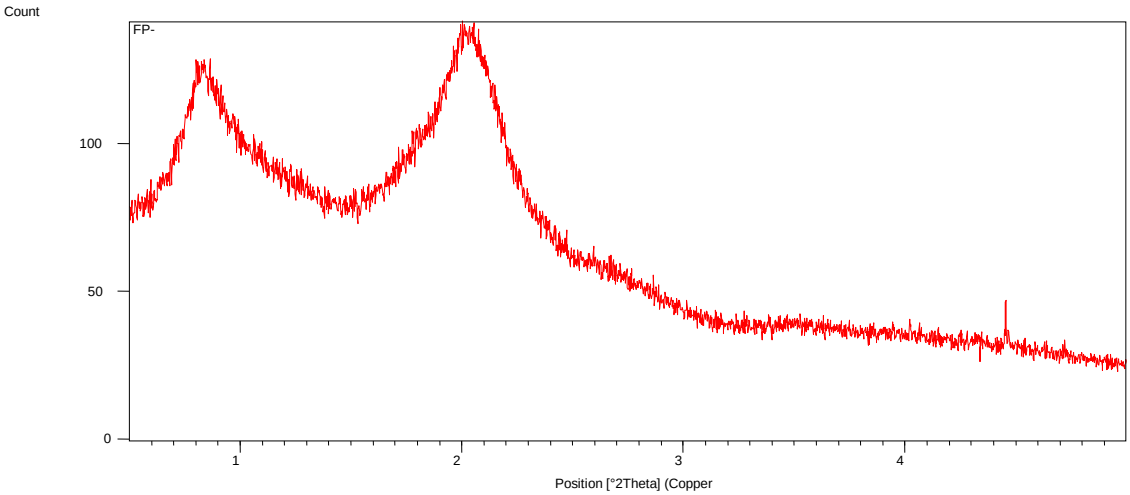

Fig. X-ray diffraction of Pitavastatin with HPMC/MC

Identification tests for tablet dosage form:

Table : Characterization of Tablet Dosage form

S.no	Hardness (kg/cm)	Wt. Variation (mg)	Disintegration Time (min)	Drug Content (%)	Percent Yield (%)
1	4.6±0.096	102.2±1.124	6.24	99.16±0.166	77.26±0.264
2	4.2±0.049	102.2±1.066	6.11	98.66±0.266	78.26±0.168
3	4.4±0.169	102.8±1.266	7 .48	99.34±0.146	82.66±0.258
4	4.4±1.026	99.4±2.568	7.02	97.14±0.208	76.66±0.306

5	4.6±0.059	102.8±1.544	6 .34	95.28±0.118	79.56±0.336
6	4.6±0.076	102.8±2.056	6. 54	98.76±0.206	82.99±0.288
7	4.8±0.088	104.8±1.358	7.28	99.66±0.118	82.46±0.178
8	4.6±0.156	104.4±2.086	6.04	98.06±0.148	78.84±0.168
9	4.4±0.169	102.8±1.448	7.28	99.84±0.258	76.46±0.248
10	3.8±0.094	104.4±2.008	6.02	97.36±0.326	84.12±0.206

Data Expressed as mean ± S.D (n=3)

Dissolution Profile

Table: Dissolution profile of Tablet Dosage Form

Mean Percentage Drug Release ± Standard deviation		
Time (min)	**Pure drug**	**Tablets**
10	6.26± 1.678	82.56±0.314
20	9.14±1.158	83.96±0.414
30	12.58±1.254	85.74±0.526
40	15.42±0.418	87.28±0.418
50	19.19±1.574	88.34±0.218
60	25.12±0.734	89.92±0.116

Data Expressed as mean ± S.D (n=3)

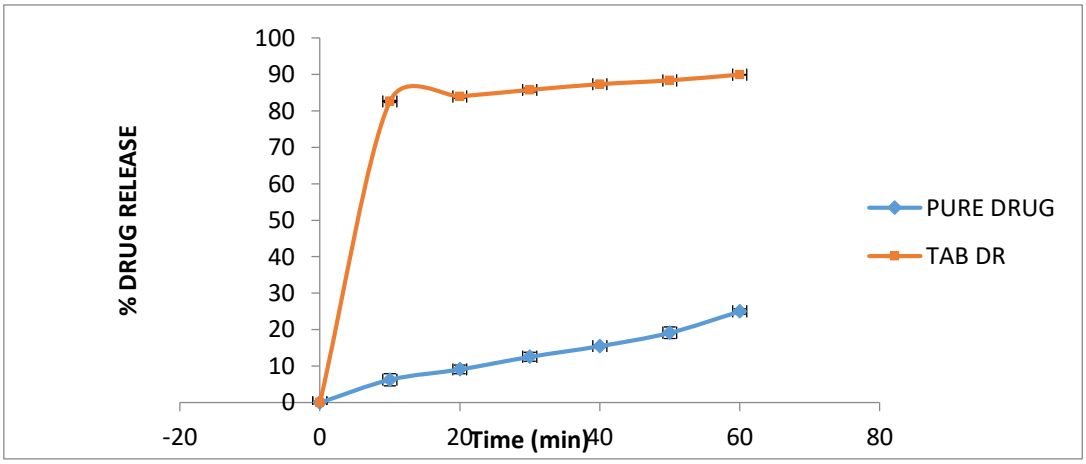

Fig : In vitro dissolution profile of Tablets Dosage form (%drug released vs time)

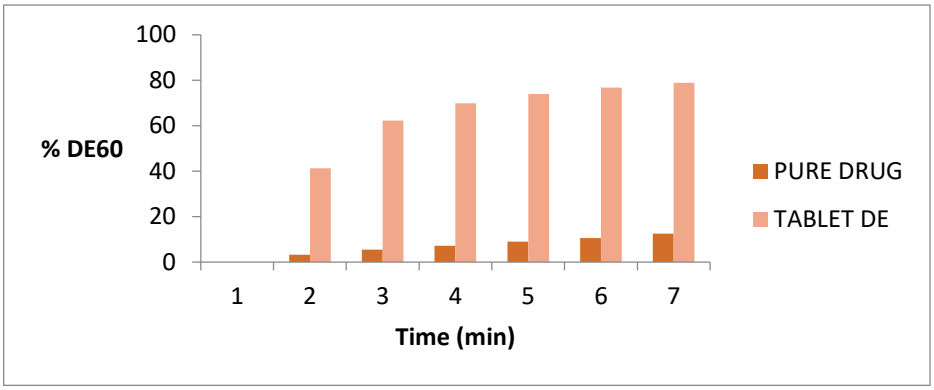

Fig : %DE60 of Tablet Dosage form

STABILITY TESTING:

Dissolution profile After Stability

Table : Dissolution profile of Tablet Dosage Form After Stability

Mean Percentage Drug Release ± Standard deviation		
Time (min)	**Pure drug**	**Tablets(After Stability)**
10	6.26± 1.678	81.42±0.318
20	9.14±1.154	82.58±0.116
30	12.58±1.268	84.36±0.218
40	15.46±0.428	85.31±0.118
50	19.18±1.574	86.36±0.326
60	25.12±0.744	88.82±0.326

Data Expressed as mean ± S.D (n=3)

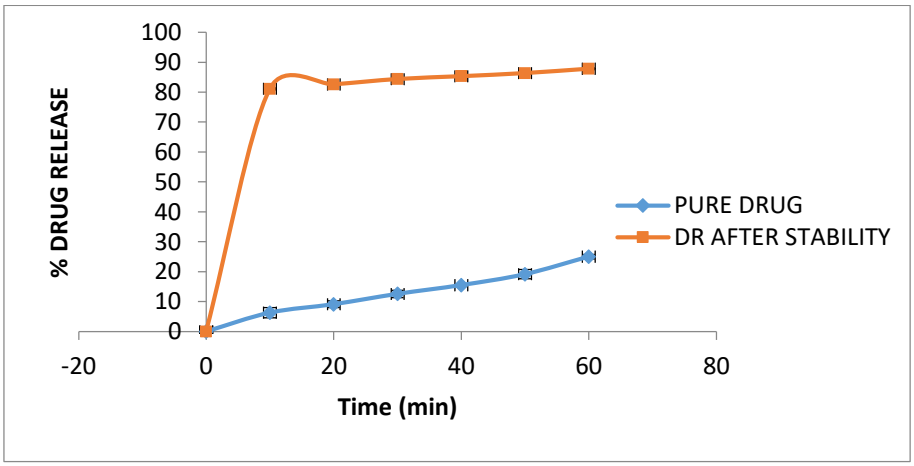

Fig :In vitro dissolution profile of Tablets Dosage form (%drug released vs time) After Stability

Table : Dissolution efficiency of Tablet Dosage form (After Stab.)

Time(min)	Dissolution Efficiency(%) PR	Dissolution Efficiency(%) TAB(After Stab.)
10	3.238	41.548
20	5.428	62.202
30	7.224	68.624
40	8.924	72.678
50	11.604	78.306
60	12.528	78.268

Data Expressed as mean ± S.D (n=3)

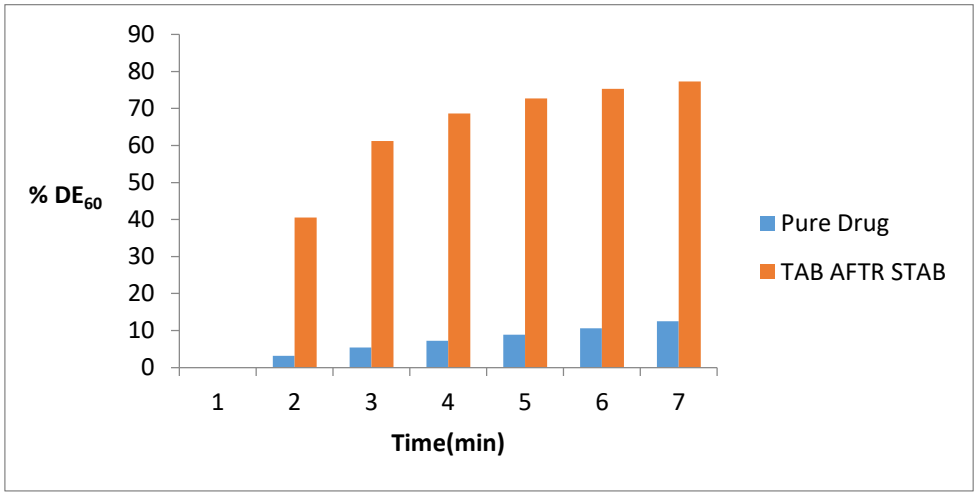

Fig : %DE60 of Tablet Dosage form(After Stability)

Conclusion:

Four ratios of drug : carrier were prepared (1:1, 1:3, 1:5, 1:7) and 1:7 was the optimized ratio which shows maximum release of drug via dissolution profile. In the present work, Solid Dispersions were prepared by Kneading technique to enhance solubility of Pitavastatin. Solid dispersions were evaluated for Fourier transform infrared spectroscopy (FTIR), thermal analysis, dissolution studies, powder X-ray diffraction (PXRD), scanning electron microscopy (SEM), and stability studies to confirm enhancement in solubility. The prepared solid dispersions are formulated into tablet dosage form and characterized by various parameters i.e. weight variation, hardness, friability, disintegration and dissolution rate. The evaluated parameters of tablet dosage form shows increase in solubility and dissolution rate of drug.

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