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ENHANCEMENT OF BIOAVAILABILITY OF ATORVASTATIN AND FENOFIBRATE COMBINATION USING SOLID DISPERSION TECHNIQUE

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ABSTRACT: The present investigation aimed to design and evaluate solid dispersions of Atorvastatin and Fenofibrate combination, to enhance the solubility and bioavailability. When used in combination, these drugs show additive beneficial effect and comparatively fewer side effects, in the treatment of Hyperlipidemia. Being members of BCS Class-II, these drugs exhibit low aqueous solubility and high permeability. The solubility of the above drug combination is increased using solid dispersions with PEG 4000 and PEG 6000 in different concentrations, using the solvent evaporation method. The *in-vitro* release profiles of prepared solid dispersions were found to exhibit better dissolution characteristics compared to that of a branded market formulation, Atocor-F. The prepared solid dispersions were evaluated concerning, percent practical yield, drug content, and characterized using Fourier Transform Infra-red (FTIR) spectroscopy, X-Ray Diffraction (XRD) and Scanning Electron Microscopy (SEM). FT-IR spectra data showed the absence of drug-polymer incompatibility. Drug-polymer interaction was investigated using X-Ray diffraction (XRD) and Scanning Electron Microscopy (SEM). The formulation F_4, containing Atorvastatin: Fenofibrate: PEG 4000: PEG 6000: 1:1:2:4 was found to show the best *In-vitro* drug release.

INTRODUCTION: [1, 2, 3] Improving oral bioavailability of drugs that are given as solid dosage forms remains a challenge for the formulation scientists owing to solubility problems. The dissolution rate could be the rate-limiting process in the absorption of a drug from a solid dosage form of relatively insoluble drugs.

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The drugs with poor aqueous solubility belong to Biopharmaceutical Classification System Class II and Class IV group of compounds and are allied with slow drug absorption leading to inadequate and variable bioavailability and G.I. mucosal toxicity of drugs.

Therefore, it is necessary to enhance the dissolution of these drugs to ensure the maximum therapeutic utility of these drugs. Before studying the various approaches to enhance dissolution, it is necessary to understand the basic process of dissolution. Dissolution is a process by which a solid substance goes into solution. The extents to which the dissolution proceeds, under a given set of

conditions, are referred to as the solubility of the substance in the solvent, *i.e.,* rate of solution (dissolution) and the amount that can be dissolved (solubility) are not same. The dissolution rate of a drug is directly proportional to its solubility as per Noyes-Whitney equation, and therefore, the solubility of a drug substance is a major factor that determines its dissolution rate and hence its absorption and bioavailability eventually. The various properties of the drug that affect drug dissolution and its rate include solubility, particle size, polymorphism, salt form, Complexation, wettability, *etc*. For complete absorption and good bioavailability of the orally administered drug, it must be dissolved in gastric fluids. Drugs with slow dissolution rates generally show erratic and incomplete absorption leading to low bioavailability when administered orally. Since, aqueous solubility and slow dissolution rate of BCS class II and class IV drugs is a major challenge in the drug development and delivery processes, improving aqueous solubility and slow dissolution of BCS Class II and Class IV drugs have been investigated extensively. Various techniques have been used in an attempt to improve solubility and dissolution rates of poorly water-soluble drugs which include solid dispersions (SD), Micronization, lipid-based formulations, melt granulation, direct compaction, solvent evaporation, coprecipitation, adsorption, ordered mixing, solvent deposition inclusion Complexation and steam aided granulation. In these techniques, the carrier plays an important role in improving the solubility and dissolution rate.

Solid Dispersions: [4, 5] The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic inert carrier or matrix and a hydrophobic drug. The carrier can be either crystalline or amorphous. Most commonly used carriers for the preparation of SDs are the different grade of polyethylene glycols (PEGs) and polyvinylpyrrolidone (PVPs), Gelucire 44/14, Labrasol, sugars, and urea. The drug can be dispersed molecularly, in amorphous particles (clusters) or crystalline particles. The first drug, whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole by Sekiguchi and Obi. Literature reviews on solid dispersion suggest that there is an increasing interest in using this approach. The Solid Dispersion Technique is one of the most successful methods for improving the dissolution and bioavailability of poorly soluble drugs because it is simple, economic, and advantageous.

Advantages of Solid Dispersions: The advantages of Solid Dispersions are as follows:

In Solid dispersions, Drugs have amorphous form, with reduced particle size, improved wettability, and higher porosity, all of which are important for better dissolution and hence, better bioavailability.

Limitations of Solid Dispersions: Although there exists a great research interest in solid dispersion, the commercial utilization is very limited. Problems of solid dispersion involve the physical and chemical stability of drugs and vehicles, method of preparation, reproducibility of its physicochemical properties, formulation of solid dispersion into dosage forms, and Scale-up of manufacturing processes.

Preparation of Solid Dispersions by Solvent Evaporation Method: [6] Tachibana and Nakamura were the two researchers who firstly applied solvent evaporation method for the preparation of solid dispersions. Drug (b-carotene) and carrier (PVP) were dissolved in a common solvent (chloroform) and the solvent was evaporated to form the solid mass. This solvent evaporation method involves two steps- first, the preparation of a solution containing both matrix material or carrier and drug and second, the removal of the solvent resulting in the formation of the solid mass. Nature of the solvent used and the rate and temperature of evaporation of the solvent are the critical factors which can affect the formed mass.

One of the major advantages of this method is that the thermal decomposition of the drugs can be prevented as the low temperature is required for the evaporation of the organic solvents. This method has several disadvantages like the high cost of preparation, difficulty in selecting a common solvent for both the drug and carrier and complete solvent removal from the product can be a lengthy process and the fact that the crystal forms are difficult to reproduce.

MATERIALS AND METHODS:

Materials Used: The Atorvastatin and Fenofibrate pure drugs were obtained as gift samples from There Dose Pharma Pvt. Ltd, Pragathi Nagar, Kukatpally, Hyderabad. The polymers, Polyethylene glycol LR-6000 and Polyethylene glycol-4000 were purchased from SD-Fine Chem. Ltd and Finar Chemicals. Ltd. The solvent, Methanol-AR, was purchased from Finar Chemicals. Ltd.

Estimation of Atorvastatin and Fenofibrate using High - Performance Liquid Chromatography (HPLC): [7, 8, 9] Accurately 20 mg of atorvastatin was weighed into 200 ml clean and dry volumetric flask, and 140 ml of methanol is added. It is sonicated for 10 min, and volume made up to mark with methanol. (Solution A). Accurately 32 mg of Fenofibrate was weighed into 200 ml clean and dry volumetric flask then 10ml of solution A was added using a pipette and 100 ml of methanol is added. It is sonicated for 10 min, and volume made up to mark with methanol (Mixed Standard) [13].

All solutions were freshly prepared before analysis. The prepared solutions were evaluated using HPLC, and the data obtained have been presented in **Table 2** and **3**.

TABLE 2: HPLC ESTIMATION OF ATORVASTATIN AND FENOFIBRATE

Atorvastatin		Fenofibrate	
Area	% Release	Area	% Release
434190	100.04	8935324	99.56
434512	100.11	8995403	100.22
435409	100.30	9095426	101.30
436422	100.50	9105332	101.45

TABLE 3: LINEARITY DATA OF ATORVASTATIN AND FENOFIBRATE

S. no.	Atorvastatin		Fenofibrate	
	Conc. (µg/ml)	Area	Conc. (µg/ml)	Area
1	1.25	49105	20	1007664
2	2.50	98209	40	2115428
3	3.75	147314	60	3022991
4	5.00	196419	80	4030655
5	6.25	255537	100	5038319

Preparation of Atorvastatin and Fenofibrate Solid Dispersions: [10] Solid Dispersions were prepared using the Solvent Evaporation method, using the carrier system in different concentration ratios **Table 1**.

TABLE 1: FORMULATION INGREDIENTS AND THEIR CONCENTRATION RATIOS

Formulation	Composition code	Ratio
F_1	Atorvastatin + Fenofibrate + PEG4000 + PEG6000	1:1:2:2
F_2	Atorvastatin + Fenofibrate + PEG4000	1:1:2
F_3	Atorvastatin + Fenofibrate + PEG6000	1:1:2
F_4	Atorvastatin + Fenofibrate+ PEG4000 + PEG6000	1:1:2:4
F_5	Atorvastatin + Fenofibrate + PEG4000 + PEG600	1:1:4:2
F_6	Atorvastatin + Fenofibrate+ PEG4000 + PEG6000	1:1:2:3
F_7	Atorvastatin + Fenofibrate+ PEG4000 + PEG6000	1:1:3:2

Solvent Evaporation Method: [11] The drug and the excipients were dissolved in sufficient volume of methanol with continuous stirring. The solvent was then completely evaporated at 40 – 45 ºC with continuous stirring to obtain dry granules. The resulting solid dispersions were stored in an airtight container until further use.

Evaluation of Atorvastatin and Fenofibrate Solid Dispersions: [12, 13, 14, 15, 16, 17, 18]

Physical Appearance: All the batches of Atorvastatin and Fenofibrate solid dispersions were evaluated for color and appearance, as shown in **Table 4**.

TABLE 4: PHYSICAL APPEARANCE OF ATORVASTATIN AND FENOFIBRATE SOLID DISPERSIONS

Formulation Code	Colour Appearance	Physical Appearance
F_1	Creamy-White	Fine Powder
F_2	Creamy-White	Fine Powder
F_3	Creamy-White	Fine Powder
F_4	Creamy-White	Fine Powder
F_5	Creamy-White	Fine Powder
F_6	Creamy-White	Fine Powder
F_7	Creamy-White	Fine Powder

Percentage Practical Yield (PY): Percentage practical yield were calculated to know about percent yield or efficiency of the solvent evaporation method. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation.

PY (%) = Practical Mass (SD) / Theoretical Mass (Drug + Carrier)] ×100

Drug Content: The Physical mixture and solid dispersion equivalent to 25 mg of the model drug

were taken and dissolved separately in 25 ml of methanol. The solutions were filtered and were further diluted such that the absorbance falls within the range of the standard curve. The absorbance of solutions was determined at 245 and 285nm by UV-Visible spectrophotometer. The actual drug content was calculated using the following equation as follows:

% Drug content = [Weight of Drug $_{(act)}$ / Weight of Drug Carrier] × 100

The data obtained have been reported in **Table 5**.

TABLE 5: DRUG CONTENT UNIFORMITY AND PERCENTAGE PRACTICAL YIELD

F. Code	Drug Content Uniformity (%)			% Practical Yield	Mean ± SD
	1st	2nd	3rd		
F_1	93.6	92.89	94.01	93.500	94.75
F_2	92.68	92.45	92.18	92.437	93.75
F_3	91.76	91.45	91.18	91.463	92.55
F_4	100.40	99.89	99.84	99.997	96.05
F_5	95.89	95.99	95.08	95.683	95.50
F_6	94.06	93.89	94.56	94.170	93.75
F_7	93.15	93.87	93.21	93.410	93.10

***In-vitro* Dissolution Study:** Dissolution studies were performed assuring sink condition according to the paddle method (USP) using USP XXIII apparatus type-II (electro lab TDT-O9T). The dissolution medium was 900 ml 0.1M SLS kept at 37 ºC ± 0.2 ºC. The solid dispersions weighing 100 mg was taken in a muslin cloth and tied to the rotating paddle kept in the basket of dissolution apparatus, the basket was rotated at 50 rpm. Samples of 5 ml were withdrawn at specified time intervals and analyzed spectrophotometrically at 245nm and 285 nm using Shimadzu-1700 UV-visible spectrophotometer; the samples withdrawn were replaced by fresh dissolution medium. Each preparation was tested in triplicate and then means values were calculated and represented in **Table 6, 7, 8, 9, 10, 11** and **12** for formulations F1, F2, F3, F4, F5, F6, and F7 respectively. The formulation showing the best dissolution profile was selected and subjected to further studies like XRD and SEM.

Infrared spectroscopy (IR): FT-IR spectra of pure drugs, carriers **Fig. 10, 11, 12** and **13** and the Solid dispersions were obtained by Bruker FT-IR spectrophotometer using potassium bromide (KBr) pellets. KBr pellets were prepared by gently mixing the sample with KBr (1:100). The sample was scanned from 4,000 to 400 cm^{-1}.

X-Ray Diffraction Study: For the selected formulation **Fig. 15** and pure drugs, the XRD patterns were recorded on an Equinox-3000 Multipurpose XRD.

SEM Study: The SEM photographs of the pure drugs **Fig. 16** and selected formulation **Fig. 17** were obtained using a Scanning Electron Microscope, JEOL-JSm6510LA, at Pharmatrain Lab, Kukatpally, Hyderabad.

DISCUSSION:

Estimation of Atorvastatin and Fenofibrate Combination using HPLC: The drug samples of Atorvastatin and Fenofibrate were estimated using HPLC **Table 2**. Also, the pure samples of Atorvastatin and Fenofibrate were estimated using HPLC and linearity for both the drugs was calculated. The linearity for Atorvastatin sample was found to be 0.999 while that of the Fenofibrate sample was found to be 0.9996 **Fig. 1** and **2**.

Evaluation of Atorvastatin and Fenofibrate Solid Dispersions:

Physical Appearance: The prepared solid dispersions of Atorvastatin and Fenofibrate were evaluated for physical Appearance. All the formulations had a creamy-white color and a fine powdery appearance **Table 4**.

Drug Content uniformity studies and Percentage Practical Yield: The Drug content uniformity and practical percentage yield were calculated for all the seven formulations of solid dispersions. Among these, the formulation F4 has shown maximum drug content uniformity (99.997%) as well as practical percentage yield (96.05%) **Table 5**.

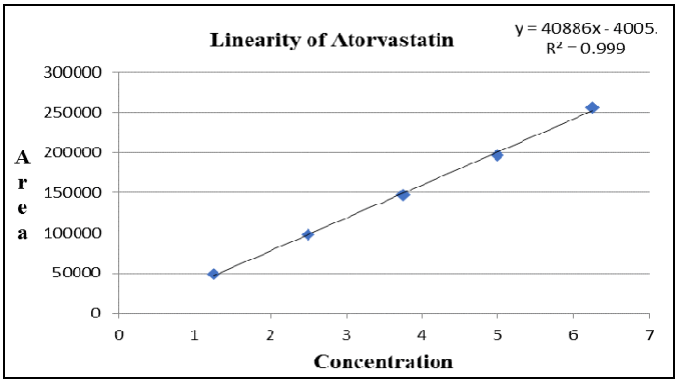

FIG. 1: LINEARITY OF ATORVASTATIN

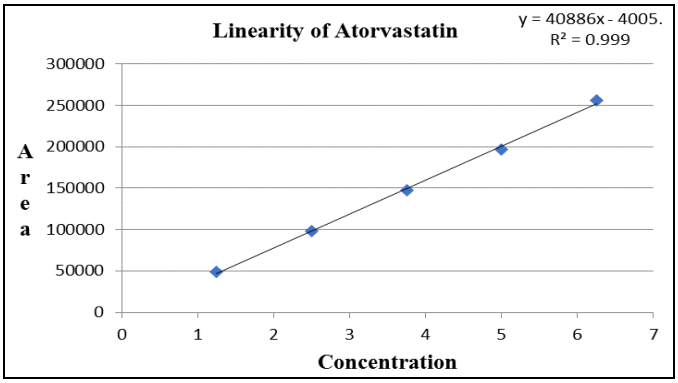

FIG. 2: LINEARITY OF FENOFIBRATE

***In-vitro* Dissolution Profiles:** The *In-vitro* dissolution of all the prepared formulations- F_1, F_2, F_3, F_4, F_5, F_6 and F_7 has been presented in **Table 6, 7, 8, 9, 10, 11** and **12** respectively, and Atocor-F® were performed in 900 ml of 0.1M SLS kept at 37 º ± 0.2 ºC and a rotation speed of 50 rpm.

TABLE 6: *IN-VITRO* DISSOLUTION PROFILE OF F_1

Time (T) (min)	$(T)^{1/2}$	logT	Cum % Drug Release*(Q)	% Drug Remaining	Log % Drug Release	Log % Drug Remaining
Atorvastatin						
00	0.000	0.000	0.000	100.00	0.000	2.000
60	7.746	1.778	84.93	15.07	1.93	1.178
120	10.95	2.079	95.17	4.83	1.97	0.683
180	13.41	2.255	97.65	2.35	1.98	0.371
240	15.49	2.380	98.68	1.32	1.99	0.120
Fenofibrate						
00	0.000	0.000	0.000	100.00	0.000	2.000
60	7.746	1.778	75.93	24.07	1.880	1.381
120	10.95	2.079	79.40	20.60	1.899	1.313
180	13.41	2.255	79.60	20.40	1.900	1.309
240	15.49	2.380	80.70	19.30	1.906	1.285

* Average of three readings

TABLE 7: *IN-VITRO* DISSOLUTION PROFILE OF F_2

Time (T) (min)	$(T)^{1/2}$	logT	Cum % Drug Release*(Q)	% Drug Remaining	Log % Drug Release	Log % Drug Remaining
Atorvastatin						
00	0.000	0.000	0.000	100.00	0.000	2.000
60	7.746	1.778	87.05	12.95	1.939	1.112
120	10.95	2.079	92.26	7.74	1.965	0.888
180	13.41	2.255	93.32	6.68	1.969	0.824
240	15.49	2.380	98.61	1.39	1.993	0.143
Fenofibrate						
00	0.000	0.000	0.000	100.00	0.000	2.000
60	7.746	1.778	43.90	56.10	1.642	1.748
120	10.95	2.079	63.20	36.80	1.800	1.565
180	13.41	2.255	74.70	25.30	1.873	1.403
240	15.49	2.380	78.63	21.37	1.895	1.329

*Average of three readings

TABLE 8: *IN-VITRO* DISSOLUTION PROFILE OF F_3

Time (T) (min)	$(T)^{1/2}$	logT	Cum % Drug Release*(Q)	% Drug Remaining	Log % Drug Release	Log % Drug Remaining
Atorvastatin						
00	0.000	0.000	0.000	100.00	0.000	2.000
60	7.746	1.778	89.51	10.49	1.951	1.020
120	10.95	2.079	93.03	6.97	1.968	0.843

180	13.41	2.255	95.65	4.35	1.980	0.638
240	15.49	2.380	99.16	0.84	1.996	-0.075
Fenofibrate						
00	0.000	0.000	0.000	100.00	0.000	2.000
60	7.746	1.778	73.90	26.10	1.868	1.416
120	10.95	2.079	82.20	17.80	1.914	1.250
180	13.41	2.255	81.36	18.64	1.910	1.270
240	15.49	2.380	85.86	14.14	1.933	1.150

*Average of three readings

TABLE 9: *IN-VITRO* DISSOLUTION PROFILE OF F_4

Time (T) (min)	$(T)^{1/2}$	logT	Cum % Drug Release*(Q)	% Drug Remaining	Log % Drug Release	Log % Drug Remaining
Atorvastatin						
00	0.000	0.000	0.000	100.00	0.000	2.000
60	7.746	1.778	95.03	4.97	1.977	0.696
120	10.95	2.079	96.51	3.49	1.984	0.542
180	13.41	2.255	99.16	0.84	1.996	-0.075
240	15.49	2.380	100.89	-0.89	2.003	0.00
Fenofibrate						
00	0.000	0.000	0.000	100.00	0.000	2.000
60	7.746	1.778	85.25	14.75	1.930	1.168
120	10.95	2.079	89.01	10.99	1.949	1.040
180	13.41	2.255	96.29	3.71	1.983	0.569
240	15.49	2.380	102.11	-2.11	2.009	0.00

*Average of three readings

TABLE 10: *IN-VITRO* DISSOLUTION PROFILE OF F_5

Time (T) (min)	$(T)^{1/2}$	logT	Cum% Drug Release(Q)	% Drug Remaining	Log % Drug Release	Log % Drug Remaining
Atorvastatin						
00	0.000	0.000	0.000	100.00	0.000	2.000
60	7.746	1.778	83.78	16.22	1.923	1.210
120	10.95	2.079	88.77	11.23	1.948	1.050
180	13.41	2.255	89.20	10.80	1.950	1.033
240	15.49	2.380	90.97	9.03	1.958	0.955
Fenofibrate						
00	0.000	0.000	0.000	100.00	0.000	2.000
60	7.746	1.778	79.40	20.60	1.899	1.313
120	10.95	2.079	35.70	64.63	1.522	1.808
180	13.41	2.255	51.60	48.40	1.712	1.684
240	15.49	2.380	24.80	75.20	1.394	1.876

*Average of three readings

TABLE 11: *IN-VITRO* DISSOLUTION PROFILE OF F_6

Time (T) (min)	$(T)^{1/2}$	logT	Cum % Drug Release*(Q)	% Drug Remaining	Log % Drug Release	Log % Drug Remaining
Atorvastatin						
00	0.000	0.000	0.000	100.00	0.000	2.000
60	7.746	1.778	81.29	18.71	1.910	1.272
120	10.95	2.079	85.70	14.30	1.932	1.155
180	13.41	2.255	90.48	9.52	1.956	0.978
240	15.49	2.380	93.16	6.84	1.969	0.835
Fenofibrate						
00	0.000	0.000	0.000	100.00	0.000	2.000
60	7.746	1.778	30.10	69.90	1.478	1.844
120	10.95	2.079	70.83	29.17	1.850	1.464
180	13.41	2.255	57.60	42.40	1.760	1.627
240	15.49	2.380	65.00	35.00	1.812	1.544

*Average of three readings

TABLE 12: *IN-VITRO* DISSOLUTION PROFILE OF F_7

Time (T) (min)	$(T)^{1/2}$	logT	Cum % Drug Release*(Q)	% Drug Remaining	Log % Drug Release	Log % Drug Remaining
Atorvastatin						
00	0.000	0.000	0.000	100.00	0.000	2.000
60	7.746	1.778	77.19	22.81	1.887	1.358
120	10.95	2.079	79.35	20.65	1.899	1.314
180	13.41	2.255	82.91	17.09	1.918	1.232
240	15.49	2.380	92.20	7.80	1.964	0.892
Fenofibrate						
00	0.000	0.000	0.000	100.00	0.000	2.000
60	7.746	1.778	26.00	74.00	1.414	1.869
120	10.95	2.079	57.20	42.80	1.757	1.631
180	13.41	2.255	38.03	61.97	1.580	1.792
240	15.49	2.380	58.00	42.00	1.763	1.623

*Average of three readings

Fig. 3 and **4** diagrammatically represent all the dissolution profiles. At the end of four hours, the formulation F_4 showed 100.89% drug release concerning Atorvastatin and 102.11% drug release concerning Fenofibrate.

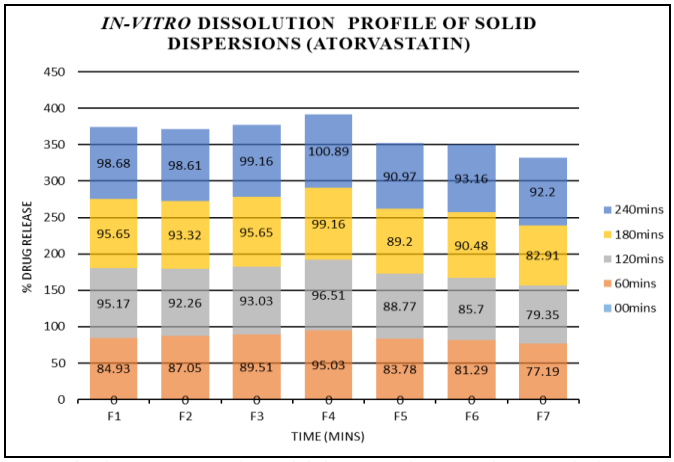

FIG. 3: *IN-VITRO* DISSOLUTION PROFILES OF SOLID DISPERSIONS WITH RESPECT TO ATORVASTATIN

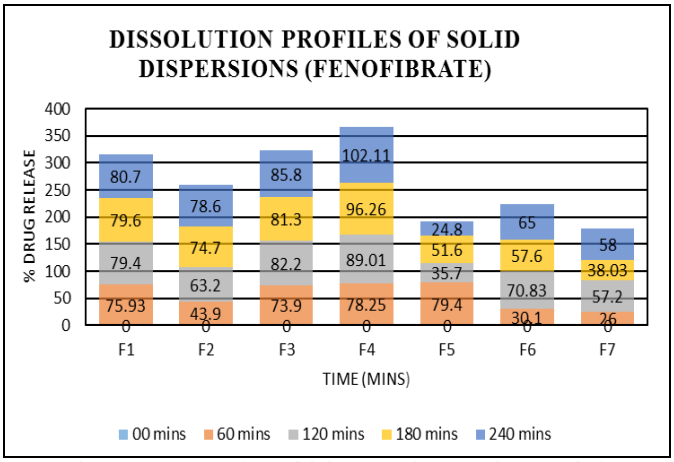

FIG. 4: *IN-VITRO* DISSOLUTION PROFILES OF THE SOLID DISPERSIONS WITH RESPECT TO FENOFIBRATE

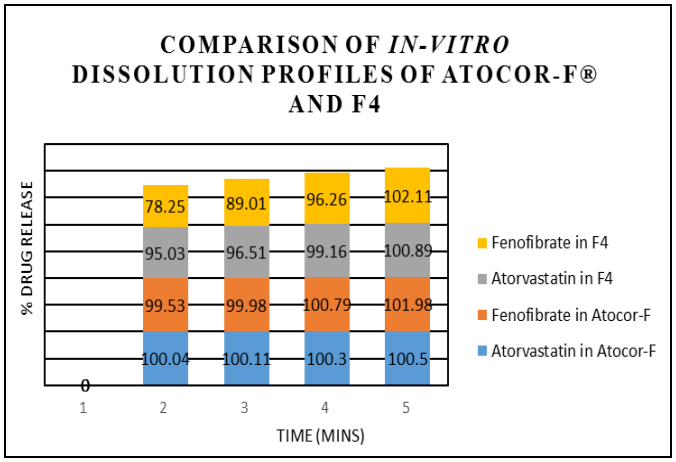

FIG. 5: COMPARISON OF *IN-VITRO* DISSOLUTION PROFILES OF F4 AND ATCOR-F

The marketed formulation, Atocor-F® showed 100.5% release concerning Atorvastatin and 101.98% concerning Fenofibrate **Fig. 5**. F_4 was found to show the best %drug release. Hence, F_4 was selected for further studies like FTIR, XRD, DSC, and SEM.

Calculation of *In-vitro* Release Kinetics: After collecting the *in-vitro* dissolution data, the release kinetics for F4 were calculated and presented in **Table 13**. Graphs were plotted for First order kinetics - % drug release *vs*. Time **Fig. 6**, Hixon Crowell model - Time *vs*. Hixon Crowell Value **Fig. 7**, Higuchi Diffusion Plot - Cumulative % drug Release *vs*. Square root of Time **Fig. 8** and Peppas Exponential Plot - log Cumulative % Drug Release *vs*. log Time **Fig. 9**.

TABLE 13: RELEASE KINETICS OF F_4

Release Rate (Q/T)	1/Q	Peppas Exponential logQ/100	Hixon Crowell Model	Modified Cube root Equation
Atorvastatin				
0	0	0	0	0
95.030	0.01052	-0.0221393	4.563	20.824
48.255	0.01036	-0.0154277	4.586	21.040
33.053	0.01008	-0.0036635	4.628	21.423
25.222	0.00991	-0.0038486	4.655	21.671
Fenofibrate				
0	0	0	0	0
8 5.250	0.01173	-0.0693052	4.401	19.369
44.505	0.01123	-0.0505642	4.464	19.935
32.096	0.01038	-0.0164188	4.583	21.008
25.527	0.00978	0.0090633	4.674	21.846

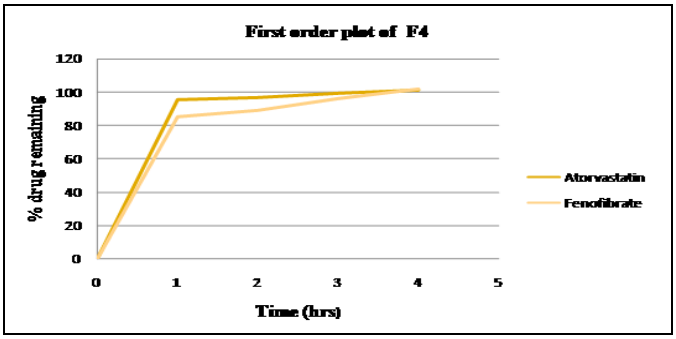

FIG. 6: FIRST ORDER RELEASE KINETICS OF F4

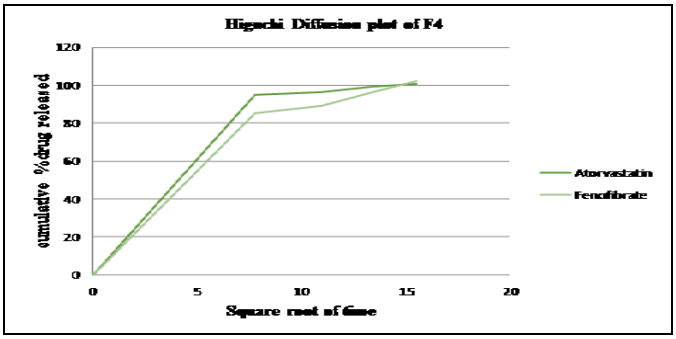

FIG. 7: HIGUCHI DIFFUSION PLOT OF F4

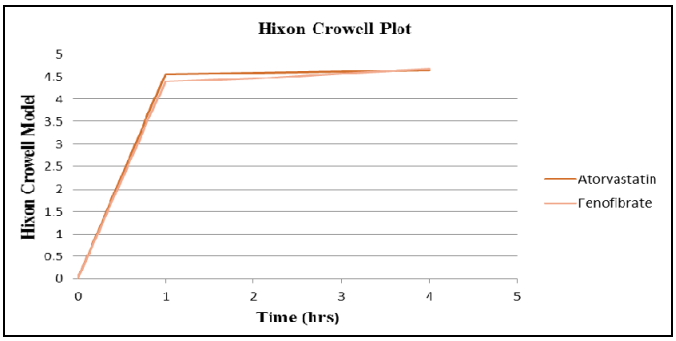

FIG. 8: HIXON-CROWELL PLOT OF F4

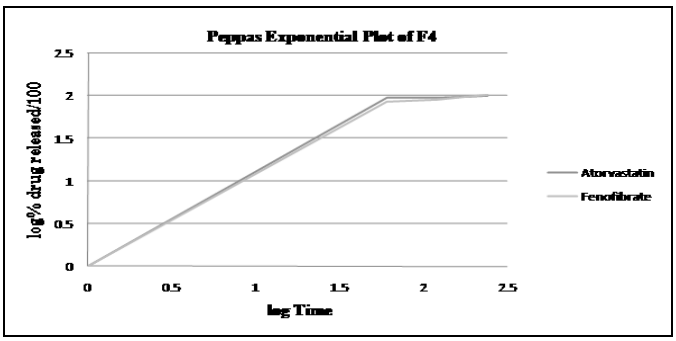

FIG. 9: PEPPAS EXPONENTIAL PLOT OF F4

The Regression Coefficient Values of all these plots were found to be around 0.9, as presented in **Table 14.**

TABLE 14: REGRESSION COEFFICIENT VALUES FOR F_4

Plot R^2	Value
Atorvastatin	
First order Plot	0.9123
Hixon Crowell Plot	0.8999
Higuchi Diffusion Plot	0.9365
Peppas Exponential Plot	0.8986
Fenofibrate	
First order Plot	0.9003
Hixon Crowell Plot	0.8987
Higuchi Diffusion Plot	0.9264
Peppas Exponential Plot	0.8990

FTIR Studies: The FTIR spectrum of F_4 **Fig. 14** was compared to the spectra of the pure samples of Atorvastatin **Fig. 10**, Fenofibrate **Fig. 11**, PEG 6000 **Fig. 12** and PEG 4000 **Fig. 13**.

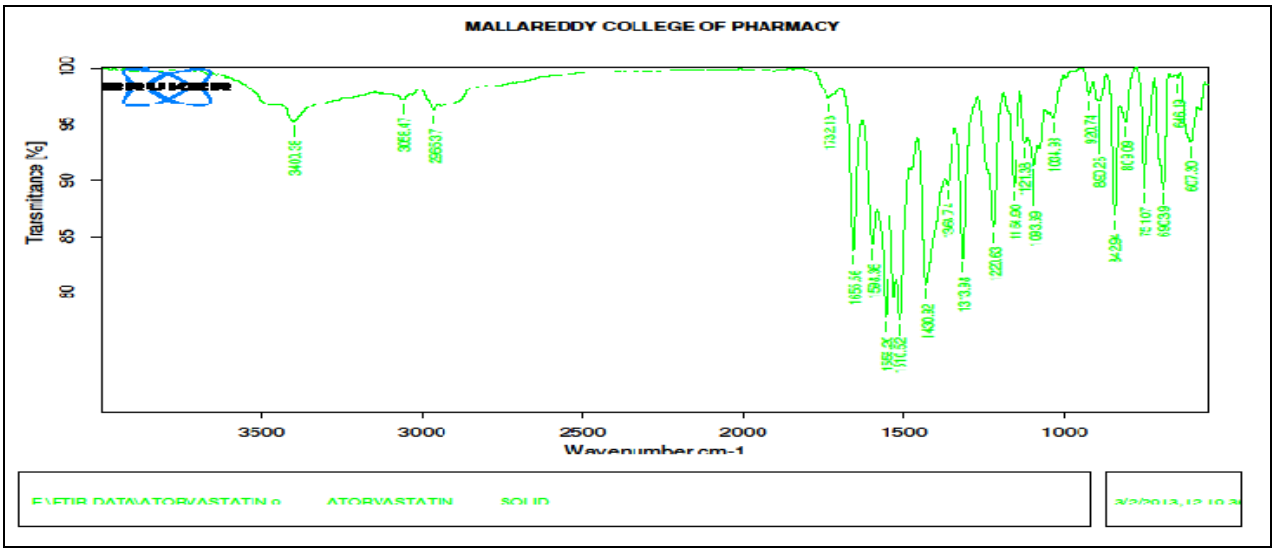

FIG. 10: FTIR OF ATORVASTATIN

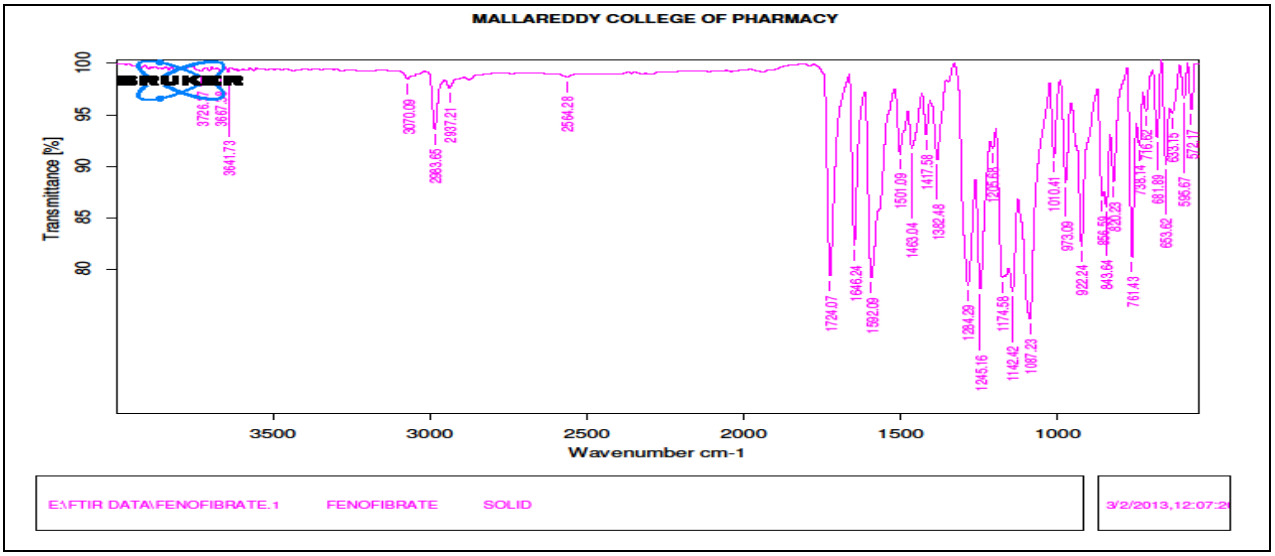

FIG. 11: FTIR OF FENOFIBRATE

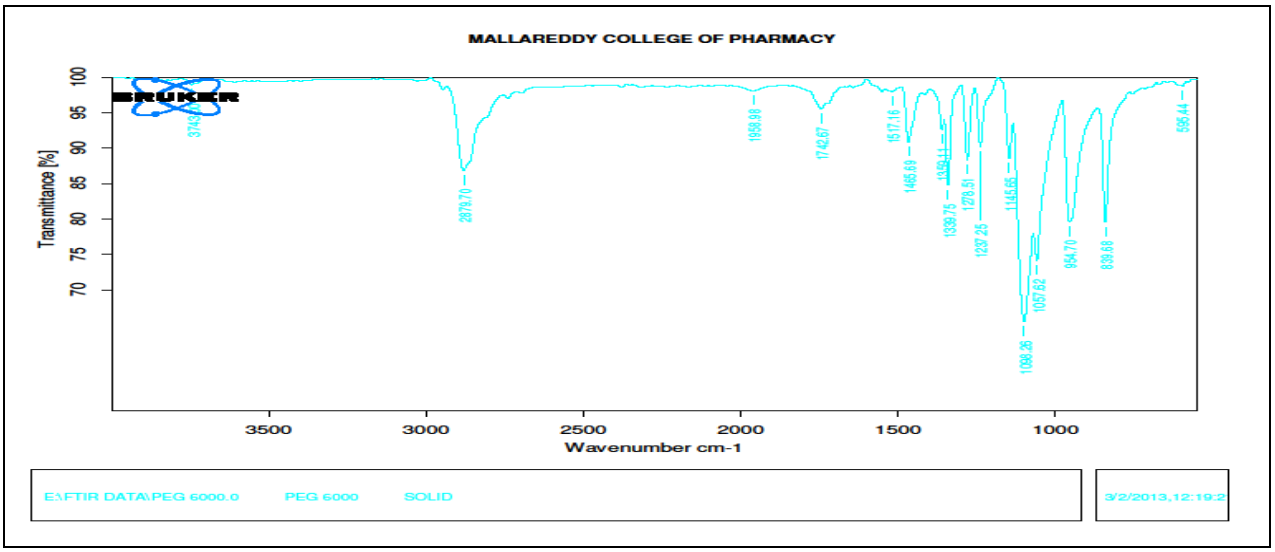

FIG. 12: FTIR OF PEG 6000

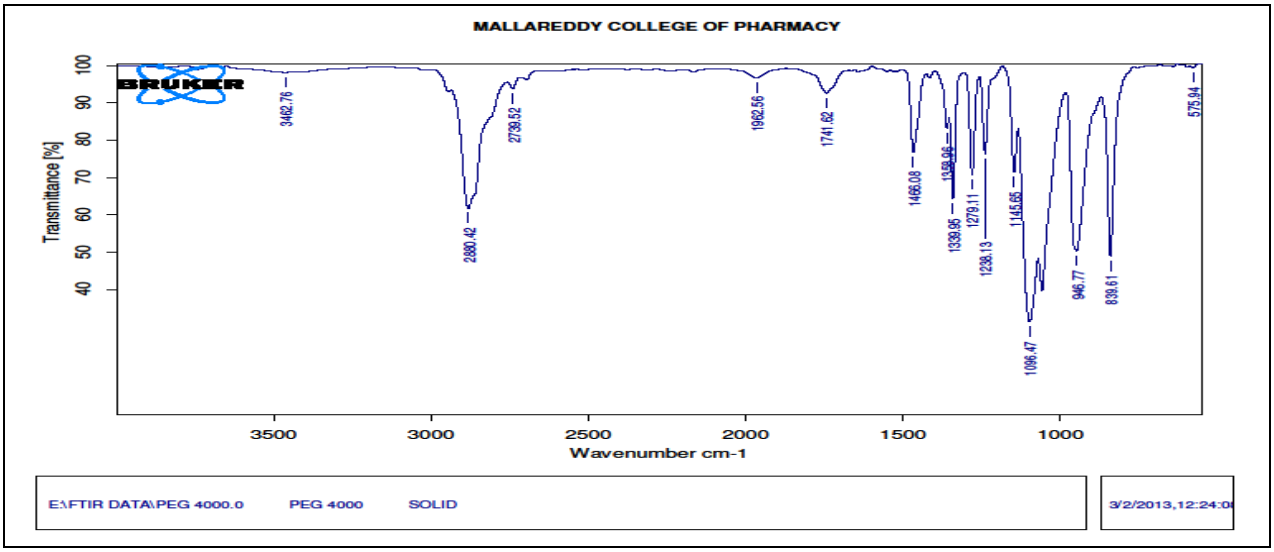

FIG. 13: FTIR OF PEG 4000

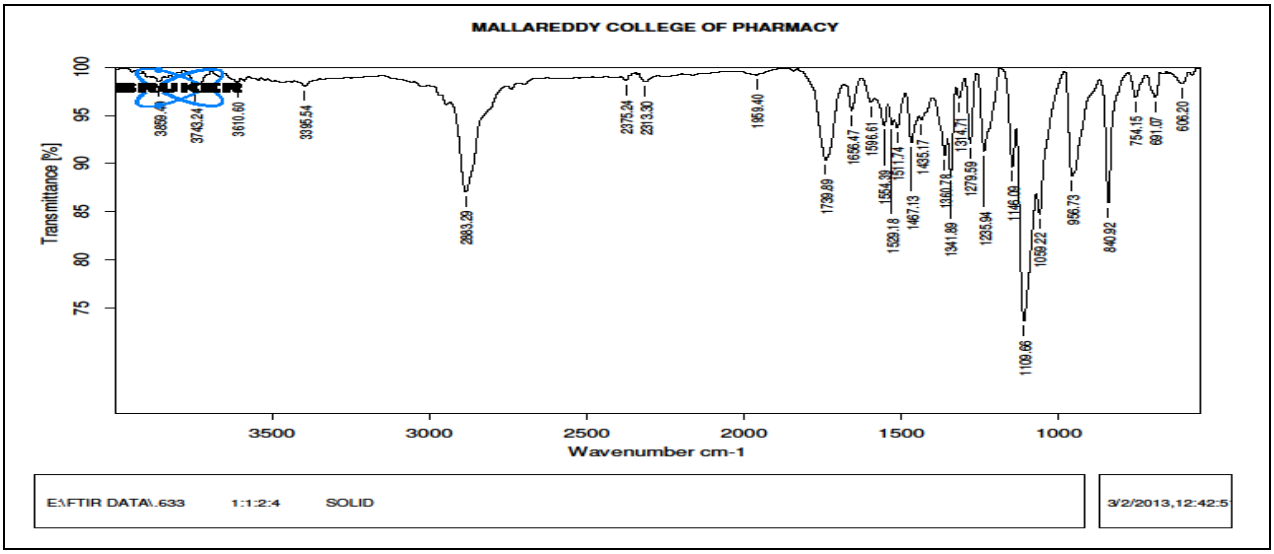

FIG. 14: FTIR OF F4

Table 15 contains the values that serve as a reference for identification of different functional groups. All the peaks in F_4 were found to be within the same range as those of the pure samples. So, it can be said that there are no incompatibilities between the drugs and excipients or in between the two drugs in the Formulation F_4.

TABLE 15: COMPARISON OF IR SPECTRA OF PURE DRUGS AND F_4

Functional Groups	Wave Number in cm^{-1}		
	Range	Pure Drugs	F_4
-N-H	3350-3180	3400.38	3395.54
$-C_6H_5$	750-690	690.39	691.07
-C=O	1680-1630	1655.56	1656.47
-OH	3670-3610	3641.73	3610.60
-COOH	1710-1680	1732.13	1739.89
-C-F	1400-1000	1093.69	1109.66
-C-Cl	760-540	751.07	754.15
$-CH_2$	2925-2850	2965.37	2883.29
$-CH_3$	1380-1260	1313.63	1341.89
-C-O	1260-1120	1156.90	1146.09

X-Ray Diffraction Study: The XRD spectrum of the formulation F_4 **Fig. 15** was compared to those of pure Atorvastatin and Fenofibrate samples.

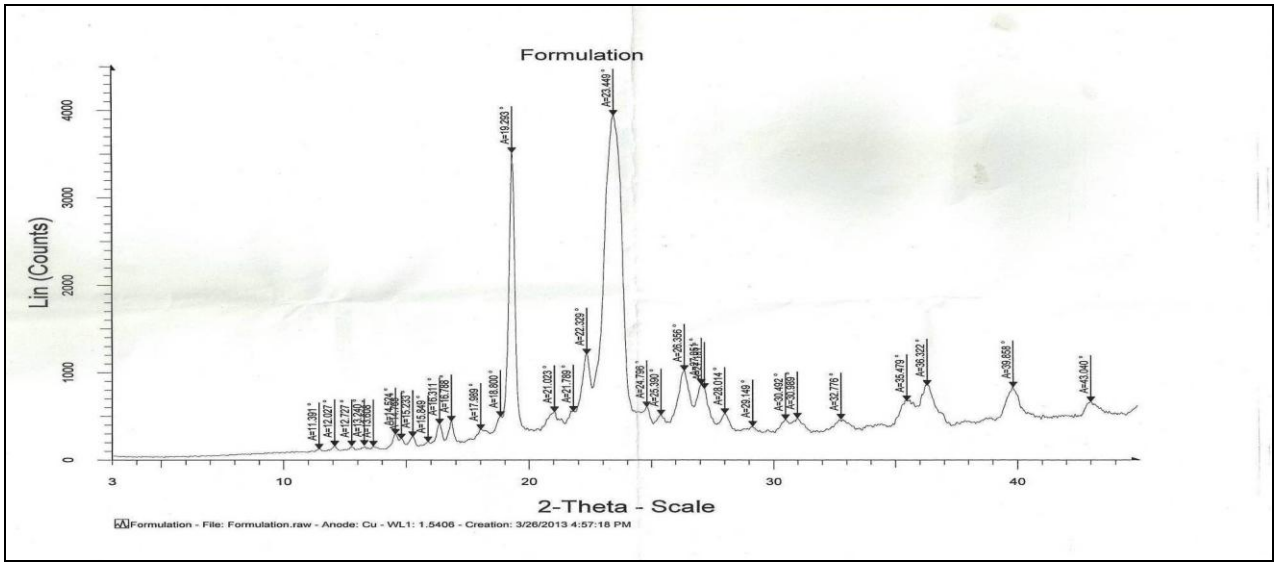

FIG. 15: XRD SPECTRUM OF F4

The values for 2θ in F4 were 23.449^{o} (Atorvastatin) and 19.293^{o} (Fenofibrate) whereas the 2θ value of Pure Atorvastatin was found to be 30.03^{o} and that of pure Fenofibrate was found to be 22.36^{o}. Hence, the observed degree of crystallinity of the drugs in F4 was relatively less when compared that observed in the pure samples.

SEM Study: The SEM study indicated that the pure drug particles were irregularly shaped and that the particles in F_4 were also irregularly shaped and evenly dispersed within the carrier system. The Solid Dispersions of F_4 were found to be within the size range of 210-350 µm **Fig. 16** & **Fig. 17.**

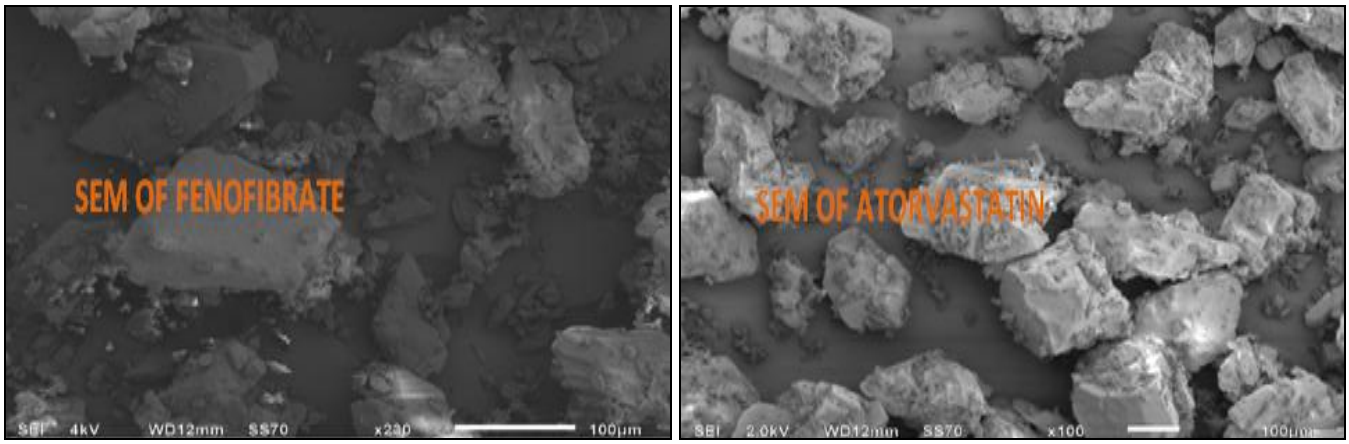

FIG. 16: SEM OF PURE ATORVASTATIN AND FENOFIBRATE

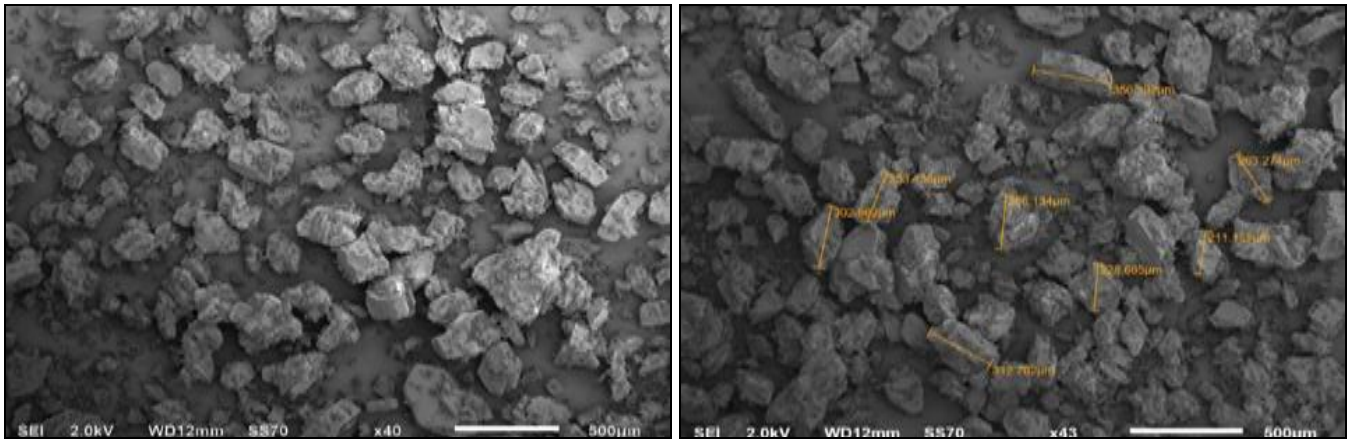

FIG. 17: SEM IMAGES OF F4

CONCLUSION: From the data obtained after the formulation and evaluation of Atorvastatin and Fenofibrate Solid Dispersions in PEG 4000 + PEG 6000 carrier system, it has been concluded that; among the seven formulations that were prepared, F_4 (Atorvastatin + Fenofibrate + PEG4000 + PEG600 = 1:1:2:4) showed the maximum percentage practical yield as well as Drug content. It also showed the best *in-vitro* dissolution profile. When compared to Atocor-F®, the formulation F_4 was found to show faster and better drug release.

FTIR studies indicated that no interactions took place between the drugs and polymers during the preparation of Solid Dispersions. The XRD spectra showed a relatively lesser degree of crystallinity in the drugs after formulation into Solid Dispersions.

SEM studies showed that the drug combination was evenly dispersed throughout the carrier system, signifying no interactions between the drugs and polymers. The drug particles were found to be irregularly shaped and in size range of 210-350µm.

Summary: Solid dispersion technology can be used to improve *in-vitro* dissolution properties of dissolution dependant poorly water-soluble drugs. In the present investigation, Atorvastatin and Fenofibrate, two poorly water-soluble Anti-hyperlipidemic agents were selected. The objective was to study the effect of different concentration ratios of carriers, PEG-4000 and PEG-6000, on *in-vitro* dissolution rate of the drug combination.

Seven Batches of solid dispersion were prepared by the solvent evaporation method. Solid dispersions of Atorvastatin and Fenofibrate combination were evaluated for physical appearance, practical percentage yield, drug content uniformity, *in-vitro* dissolution rate, FTIR, XRD, and SEM studies. It was concluded that the dissolution rate of the drug combination in F_4 solid dispersions was higher than that of Atocor-F®.

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CONFLICT OF INTEREST: Nil

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