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Preparation, Characterization and In-Vitro Evaluation of Atorvastatin Calcium Solid Dispersions with Various Hydrophilic Polymers and Its FDT Formulation.

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Abstract
The aim of the present research was to improve the solubility and hence enhance the dissolution of hydrophobic drug Atorvastatin calcium (ATV) in order to increase its bioavailability. Solid dispersion of atorvastatin calcium using various carriers like PEG 4000, PEG 6000, PVP K30, Poloxamer 407 were formulated in different ratios by fusion and solvent evaporation method. The formulations were then evaluated to choose the best carrier which showed enhanced dissolution rate in phosphate buffer (pH 6.8). The best dissolution results were with Poloxamer 407 in the ratio of 1:2. The solid dispersion formulated with Poloxamer 407 carrier was further developed into fast dissolving tablet and evaluated for in vitro dissolution, drug content analysis and disintegration time. Results showed that the FDT made with the formulated solid dispersion (Poloxamer 407 ratio 1:2) showed enhanced dissolution within a quick time.

Key Words
Solid dispersion, Fast dissolving tablet, Poorly water soluble drug, Solubility, Dissolution.

Introduction
Hypercholesterolemia is a condition characterized by very high levels of cholesterol in the blood. People with hypercholesterolemia have a high risk of developing a form of heart disease called coronary artery disease. More than 34 million American adults have elevated blood cholesterol levels (higher than 240 mg/dL).[1]Atorvastatin calcium is the drug used for treating hypercholesterolemia. Oral route is the simplest and easiest way of administering drug for reasons of convenience of administration, greater stability, smaller bulk, accurate dosage, easy production and easy compliance.[2] Therefore, most of the new chemical entities (NCE) under development these days are intended to be used as a solid dosage form that reproduces an effective in vivo plasma concentration after oral administration.[3, 4] Most of the potential drug candidates exhibit a problem of low oral bioavailability. Orally taken drugs have poor bioavailability because of poor drug dissolution and solubility rather than limited permeation through the epithelia of gastrointestinal tract. Hence, together with permeability, the solubility and dissolution behaviour of a drug are key determinants of its bioavailability when administered orally. Among various techniques employed to increase aqueous Solubility/dissolution rate, the formulation of solid dispersion is one of the most popular ones, [5, 6, 7, 8] although few marketed products rely on this concept. The solid dispersion approach frequently improves bioavailability that is limited or rate controlled by dissolution[9]. Different polymers, sugars, disintegrant and surfactants have been used as hydrophilic carriers in solid dispersion. The improved aqueous solubility/dissolution properties of solid dispersion have various mechanisms related to it including reduction of the particle size of the incorporated drug, partial transformation of the crystalline drug to the amorphous state, formation of solid solutions, formation of complexes, reduction of aggregation and agglomeration, improved wetting of the drug and solubilization of the drug by the carrier at the diffusion layer [6, 10-12]. Atorvastatin calcium (ATV), a hypolipidemic drug, is a classical example of one such drug exhibiting low solubility. It is very slightly soluble in distilled water, pH 7.4, phosphate buffer, and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.[13] Only 15-30% of oral dose is bioavailable due to its extensive presystemic metabolism (The major metabolites much less active than parent compound). Moreover, it has pH dependent solubility as well as least soluble in acidic pH and its solubility is increased on increase in pH. As it is least ionizable at pH 4.5 to 6, it is mostly in neutral form at salivary pH and facilitates absorption

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from oral cavity.[14, 15] The present investigation was focused on exploring PVP, PEG and Poloxamer 407 as carriers to increase the dissolution rate of the drug by formation of solid dispersions. Also studied was the effect of solid dispersion technique (solvent evaporation, fusion, co-grinding) on dissolution of Atorvastatin calcium. Poloxamer 407 belongs to the surfactant class and showed good dissolution results. The utility of the surfactant systems in solubilization is well known. Surfactant reduces hydrophobicity of drug by reducing interfacial or surface tension.[16] Also the solid dispersion was then formulated into FDT and evaluated under the frame of improvement of solubility to achieve better bioavailability of the drug.

Materials and Methods

Chemicals

Atorvastatin calcium was a gift sample from Alkem Laboratories, Baddi Ltd. Polyvinyl pyrrolidine (PVP K-30) was procured from CDH (New Delhi). Micro Crystalline Cellulose was procured from Abbott Pharma, Baddi, India, Cross Povidone, Sodium starch glycolate, Mannitol, Cross Carmellose Sodium were purchased from S.D. Fine Chemicals Ltd., Mumbai, India. PEG 4000, PEG 6000 purchased from Loba Chemie Pvt Ltd. (Mumbai), India, Colloidal Silicon dioxide, Talcum powder, Magnesium stearate and Lactose were purchased from S.D. Fine Chemicals Ltd., Mumbai, India. All other chemicals used in the present study were of AR Grade.

Preparation and evaluation of solid dispersions

Preparation of physical mixture

Physical mixture (PM) of ATV was prepared by mixing accurately weighed amounts of ATV with each carrier i.e. PVP K30, PXM 407, PEG 4000, and PEG 6000 in the ratio of 1:1, 1:2, 1:3 and 1:5. The physical mixture was prepared by geometric dilution method with the help of a spatula for 10 minutes. [16, 17]

Preparation of ATV solid dispersion

Solid dispersions containing different drug to polymer (carrier) ratios were prepared using solvent evaporation method and fusion method. [18, 19-21]

Solvent Evaporation Method

a) The required amount of ATV (10mg) and carriers in the ratio of 1:1, 1:2, 1:3, and 1:5 were dissolved in sufficient amount of methanol with continuous stirring in china dish. The solvent from the solution was removed at 45°C with continuous stirring to obtain dry mass. Dried mass was pulverized through 40'mesh sieve and stored in dessicator until used for further studies.
b) The required amount of ATV (10mg) and carriers in the ratio of 1:1, 1:2, 1:3, and 1:5 were dissolved in sufficient amount of methanol. The solution was mixed with constant stirring. Solvent was removed under vacuum at 45°C using rotary evaporator. Dried mass was passed through 40' mesh sieve and stored in a dessicator for further use. The yield obtained was better then 1(a).

Fusion method

Also the required amount of ATV (10mg) with various carriers in the ratio of 1:1, 1:2, 1:3 and 1:5 were prepared by melting method. In this method the polymer is melted at over a thermostatically controlled hot plate at its respective melting point and the drug was incorporated into the molten carrier mass. The blend was heated at the corresponding temperature for 5 minutes, followed by flash cooling on an ice bath. The solid dispersions thus obtained, were dried in oven at 30°C to remove moisture if present. The dried solid dispersion was pulverized through 40'mesh sieve and stored in the dessicator for further use. The dispersions obtained were tacky.

Preformulation parameters

Determination of solubility of drug

Drug solubility studies were performed in triplicate by adding excess amount of ATV to distilled water and buffer solutions having different pH (1.2, 4.5, 6.8, and 7.5). Solutions containing flasks were kept on a Rotary Shaking Incubator for 24 hrs. After 24 hrs, solutions were analysed using UV spectrophotometer (Systronic 2202, Ahmedabad, India) at 246 nm [22]

Compatibility of excipients

Fourier transform infrared spectroscopy was employed to characterize the possible interactions between the drug and carriers. In this study pure drug, physical mixture, solid dispersions were studied by ATR FTIR spectrophotometer (Bruker IFS 66/S, Germany). [18]

Solubility Analysis

The prepared solid dispersions and physical mixtures were checked for their solubility analysis according to method reported by Higuchi and Connors. An accurately weighed amount of solid dispersion

equivalent to 10mg was dissolved in 50 ml of volumetric flask containing phosphate buffer (pH 6.8). The flasks were shaken for 48 hours at 37 ± 1ºC. After 48 hours, the solutions were filtered through whatman filter paper. The filtered solution was diluted properly with methanol. The diluted solutions were analysed for ATV in UV spectrophotometer (Systronic 2202, Ahmedabad, India) at 246 nm. The solid dispersions were screened for their solubility and the ratios of the solid dispersions showing maximum solubility were further evaluated. [23]

Evaluation of Solid Dispersion

Drug content analysis of solid dispersed ATV

An accurately weighed quantity of solid dispersion equivalent to 10mg of ATV was taken and dissolved in minimum quantity of methanol and volume was made upto 50 ml. From this 1ml of solution was taken and further diluted 10 times with methanol. The solution was assayed for drug content using UV spectrophotometry method by measuring the absorbance at 246 nm. [24]

In-vitro dissolution study solid dispersed ATV

In vitro dissolution studies of the pure drug (ATV), the selected ratios of solid dispersions and physical mixtures (equivalent to 10mg ATV filled in hard gelatin capsules using stainless steel sinkers) were performed using USP type II (Paddle) apparatus (Lab India DS 8000, Pune, India) with paddle rotating at 75 rpm in 900ml of phosphate buffer pH 6.8 at 37 ± 0.5ºC. At fixed time intervals, 5ml samples were withdrawn, filtered and replaced with phosphate buffer pH 6.8. Concentration of ATV in each sample was determined by UV spectrophotometer (Systronic 2202, Ahmedabad, India) using standard curve equation. Each test was performed in triplicate upto 3 hrs. [25, 26]

FTIR studies

FTIR studies were carried out for pure drug, physical mixtures and solid dispersions. Instrument used was ATR FTIR spectrophotometer (Bruker IFS 66/S, Germany). The powdered sample was intimately mixed with dry powdered potassium bromide. The mixture was then compressed into transparent disc under high pressure using special dies. The disc was placed in IR spectrophotometer using sample holder and spectrum was recorded.

SEM studies

Sample of the Solid dispersion formulation was mounted onto the stubs using double sided adhesive tape and then coated with gold palladium alloy (150-200Å) using fine coat ion sputter,(Joel fine coat ion sputter, JFC-1100). The sample was subsequently analysed under the Scanning Electron Microscope (JSM-6100 SEM, Punjab University) for external morphology.

DSC studies

DSC studies were carried out between the active ingredient and other excipients used in the preparation of tablet formulation so as to check any kind of incompatibilities that may give rise to changes in the stability, solubility, dissolution rate and bioavailability of drug.

XRD

The powder X-ray diffraction patterns were traced employing X-Ray diffractometer (XPERT-PRO PW3050/60 Goniometer Punjab University) for the samples using Ni filtered Cu (K-α) radiation, a voltage of 45 KV, a current of 40 mA. The samples were analysed over 2θ range of 0-50º with scan step size of 0.0170º (2θ) and scan step time 25 S.

Preparation and evaluation of FDT containing solid dispersed ATV

Preparation of FDT

The best solid dispersed form of ATV was chosen and formulated into FDT. Different trial formulations (F-1 to F-6) were prepared using two different superdisintegrants and other excipients for solid dispersed ATV (equivalent to 10 mg ATV). The compositions of all the trial formulations are given in Table 2 below. FDT were prepared by direct compression method, first of all the solid dispersed ATV, filler, and other excipients were blended together for some time (10 min) after passing all the materials through 60 mesh screen and mixed with magnesium stearate and talc. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 150 mg using single punch tablet machine (A.K. Industries, Nakodar; Punjab, India) and the average hardness of 4 kg/sq.cm was obtained. A batch of 40 tablets was prepared for all the designed formulations.

Evaluation of FDT containing solid dispersed ATV

Physical property of FDT containing solid dispersed ATV

The FDT's prepared were characterised for weight variation, friability, hardness and thickness test. In weight variation test 20 tablets were selected at

random and weighed individually within each designed formulation batches. The individual weights were compared with the average weight for determination of weight variation. Friability was determined using 10 tablets in a Digital friabilator (Model 102 EI products, Panchkula, India) for 4 min at a speed of 25 rpm. Hardness of 10 tablets was also evaluated using a Monsanto

Drug content of FDT containing solid dispersed ATV

For content uniformity test, 10 tablets were weighed and powdered. The powder equivalent to 10 mg of ATV was dissolved in about 10 ml of methanol and transferred into 100 ml of volumetric flask and volume was made up using phosphate buffer (pH 6.8) and the solution was filtered using (Whatmann No. 1 filter paper). The ATV content in the filtrate was determined by measuring the absorbance at 246 nm using UV spectrophotometer (Systronic 2202, Ahmedabad, India) after appropriate dilution with phosphate buffer (pH 6.8). The drug content was determined using the standard calibration curve.

Disintegration study of FDT containing solid dispersed ATV

Disintegration time is one major parameter in development of fast dissolving tablets. Disintegration time of the prepared tablet was measured individually on six tablets in distilled water of pH 6.8 at (37±0.5) ºC and following other parameters as described in Indian Pharmacopeia using USP disintegration apparatus. [27]

In-vitro drug release study of FDT containing solid dispersed ATV

The in-vitro drug release studies of solid dispersed ATV from fast dissolving tablets were carried out using USP dissolution test apparatus type-II, Paddle type (Lab India DS 8000, Pune, India) , using 900 ml of phosphate buffer (pH 6.8) as the medium and the paddle rotating at 70 rpm for 90 minutes at 37 ± 0.5 ºC . In this test 6 tablets from each formulation batch was used for the dissolution studies. 5 ml of aliquot were withdrawn at an interval of 5min, 10 min, 15 min, 30 min, 45min, and 60 min with replacement of 5 ml fresh media. The absorbance of the resulting solution was measured at the 246 nm using UV spectrophotometer (Systronic 2202, Ahmedabad, India).

Result and Discussion

Standard graph

Standard graph of Atorvastatin Calcium was made in phosphate buffer (pH 6.8). A simple reproducible method was carried out to prepare the standard graph of ATV, accurately weighed amount of ATV (10mg) was first dissolved in 10 ml of organic solvent (methanol) and then this solution was transferred to 100 ml volumetric flask and the volume was made up with phosphate buffer (pH 6.8). Estimation of ATV was done at 246 nm using UV spectrophotometer taking phosphate buffer (pH 6.8) as blank with dilutions ranging between 6-20 µg/ml (given in Table 3. below). Appropriate dilutions were done with phosphate buffer. The standard graph obtained was linear ad had regression coefficient 0.999. (Shown in Fig. 1)

Evaluation of solid dispersed ATV

Drug content analysis

Drug content analysis of all the prepared sixteen formulations was done and the range was 89.6% to 99%. Amongst all the formulation S14th formulation contained the maximum amount of drug. Table 5 shows the drug content of all the prepared solid dispersion formulations.

Solubility studies of solid dispersed ATV

Solubility analysis of physical mixtures and solid dispersed ATV with different carriers and ratios were conducted and formulation number S14th showed the highest solubility in phosphate buffer (pH 6.8).

According to percentage of drug release and solubility analysis, the ratios of solid dispersion chosen were (1:1) for PEG 4000, (1:3) for PEG 6000 and (1:2) for PVP K30 and PXM 407.

Dissolution studies

Comparative in-vitro dissolution profile of the pure drug and the best chosen ratios of solid dispersed ATV with different carriers are given in Fig 2. Dissolution profile and data shows the change in release rate of atorvastatin calcium in pure form and in solid dispersed form the Table 6 it was clearly observed that there has been an increase in dissolution rate of all the ratios chosen as compared to the pure drug, but the solid dispersion prepared with carrier PXM in ratio of 1:2 showed the fastest release.

FTIR Analytical Studies

FTIR studies of the pure drug; PXM 407 polymer, its physical mixture and solid dispersion PXM 407 (1:2) were conducted and are shown in Figure 3,4,5,6. The prominent peaks of atorvastatin was observed (Figure 3) the region of 3365.84 cm-1 due to the (-OH stretching), a peak at 3200.12 cm-1 due to the N-H stretching and a peak at 1660.14 cm-1 was observed due to the carbonyl group. At the lower frequencies 1317.56 (C-N stretching), 1108 cm-1 (C-O stretching) 1218 cm-1 for (C-F stretching) was observed. The IR spectrum of poloxamer 407 (Fig. 4) is characterized by principal absorption peaks at 2891 cm–1 (C-H stretch aliphatic), 1342.28 cm–1 (in-plane O-H bend) and 1112 cm–1 (C-O stretch) found consistent in all binary systems with the drug.

The IR spectrum of the physical mixture (Fig. 5) displayed the superimposition pattern of atorvastatin and polymer peaks with decreased peak intensity and little shifting of the peaks. IR spectrum of solid dispersion (Figure 6) of the drug and poloxamer 407 shows overlapping of O-H and N-H group and broadening of the peak was observed. The peak was also shifted to higher wavelength 3743.96 may be due to presence of higher O-H groups in poloxamer 407. Other peaks related to C-H, C-O, C-N, stretching, remain unchanged.

XRD studies

The diffraction patterns of pure atorvastatin, poloxamer 407 and solid dispersion (S14) (1:2) are shown in Fig 8 (a), (b), (c). The diffraction pattern of pure atorvastatin showed that the drug was of crystalline nature, as demonstrated by numerous distinct peaks. Atorvastatin's numerous diffraction peaks were observed at 2θ 6.00, 9.02, 10.13, 10.42, 11.71, 12.05, 13.75, 15.09, 16.90, 17.76, 18.15, 18.67, 19.33, 19.75, 20.47, 21.48, 21.85, 22.58, 23.18, 23.60, 24.27, 25.04, 26.25, 27.39 etc. (fingerprint region), indicating the crystalline nature of atorvastatin. Polymer poloxamer 407 showed two peaks with highest intensity at 2θ of 19.07 and 23.15. Solid dispersion showed peaks of the drug; however, the intensity of the peaks was reduced when compared to that of the drug and hence absent. The results indicate that the drug in solid dispersion was amorphous as compared to the pure drug; hence the dissolution of the drug was improved. Poloxamer 407 peaks in solid dispersion were the same and just superimposed, which ruled out the possibility of chemical interaction between atorvastatin and poloxamer 407.

SEM studies

SEM study showed that pure drug particles were irregular in shape (Fig 9 a), while the physical mixture of the drug and carrier shows that drug particle remains dispersed and physically adsorbed on the surface of carrier particles (Fig 9 b). The solid dispersion of Atorvastatin with Poloxamer 407 showed homogeneous dispersion, which indicates that the atorvastatin drug molecules were uniformly dispersed into the polymer (Poloxamer 407) matrices in the ratio of 1:2 (Fig 9 c).

DSC studies

DSC thermograms of atorvastatin showing two endothermic peak one of which at 160.45˚C corresponding to the melting point of the atorvastatin and another at 63.04˚C due to loss of water or dehydration was shown in (Fig 10). The thermal behaviour of poloxamer 407 exhibited a sharp but slightly broad endothermic peak at 59.64°C and solid dispersion (S14) showed a single sharp melting peak 57.31°C, respectively (Fig 10 (a) and 10 (b). The atorvastatin melting peak in Solid dispersion was completely disappeared which attributed that the drug was completely miscible in the melted carrier and the drug was present in amorphous form.

Evaluation of Fast disintegrating tablets of ATV

Physical properties and drug content of fast dissolving tablet containing solid dispersed ATV

All the physical parameters were evaluated and were found to be within the acceptable limits, and the drug content was found to be within the range of 92.16%±0.15 to 97.36%±0.14. As the Table 7 shows all the physical parameters evaluated with % drug content, it was found that F2 formulation showed the best results out of all the other formulations.

Disintegration study of FDT containing Solid dispersed ATV

All the formulations disintegrated within 1 minute and the F2 and F3 formulations showed almost similar disintegration time. Two different disintegrants in different concentration were used and it was seen that Cross Povidone and Cross Carmellose showed different disintegration time. Cross povidone showed decrease in disintegration time with increase in its concentration but in case of cross carmellose increase in its concentration showed no effect on the disintegration time.

Dissolution study of FDT containing solid dispersed ATV

In vitro dissolution of all the prepared FDT formulations was conducted and the dissolution data obtained reported that F2 formulation showed the maximum release in 30 min of about 94.93 % and hence F2 formulation came out to be the best formulation among the others (Fig.13). So, the F2 formulation was further compared to the market formulation for its in vitro dissolution release. (Given in Figure 14 and dissolution data in Table 9)

Conclusion

From the above studies, it was concluded that the solid dispersions of the drug (Atorvastatin calcium) formulated with the use of various water soluble carriers like (PEG 4000, PEG 6000, PVP K30, and Poloxamer 407) in their different ratios prepared with different techniques like solvent evaporation method and fusion method showed enhanced solubility and dissolution characteristics in one or many factors. Solubility studies showed increase in solubility of drug in the various carriers used in the study. All the solid dispersions showed enhanced dissolution as compared to the pure drug, however, Poloxamer 407 came out as the most promising carrier. Various compatibility tests like XRD showed amorphous pattern of the solid dispersed ATV, FTIR studies showed no evidence of any chemical interactions between drug and the carrier and DSC studies further provided useful information about the drug and carrier compatibility studies. The best chosen solid dispersed ATV in best obtained ratio was further formulated into FDT and it showed increased dissolution as compared to the market formulation.

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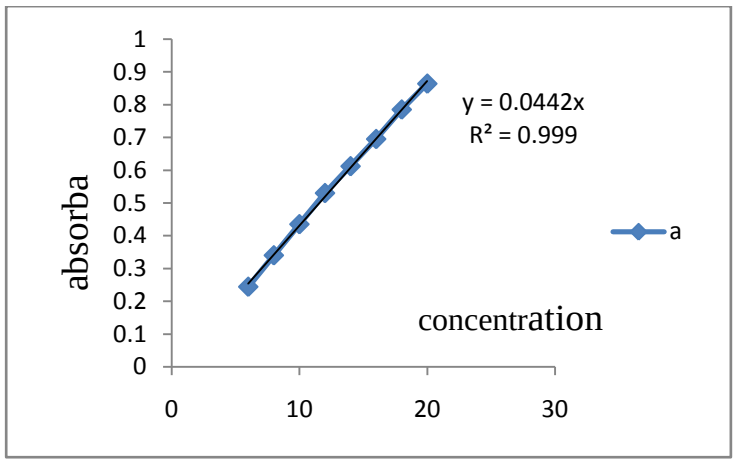


Fig. 1: Standard graph of Atorvastatin calcium.

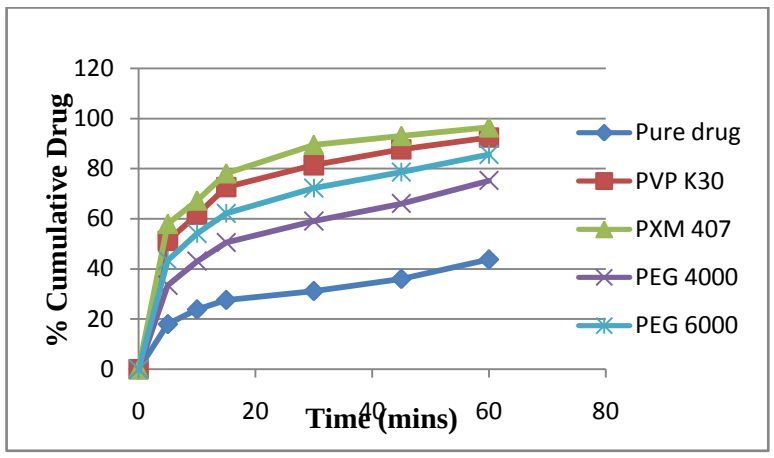


Fig 2: Comparative In-Vitro Dissolution profile of pure drug, chosen solid dispersion ratio PEG 4000 (1:1), PEG 6000 (1:3) and PVP K30 (1:2), PXM 407 (1:2)

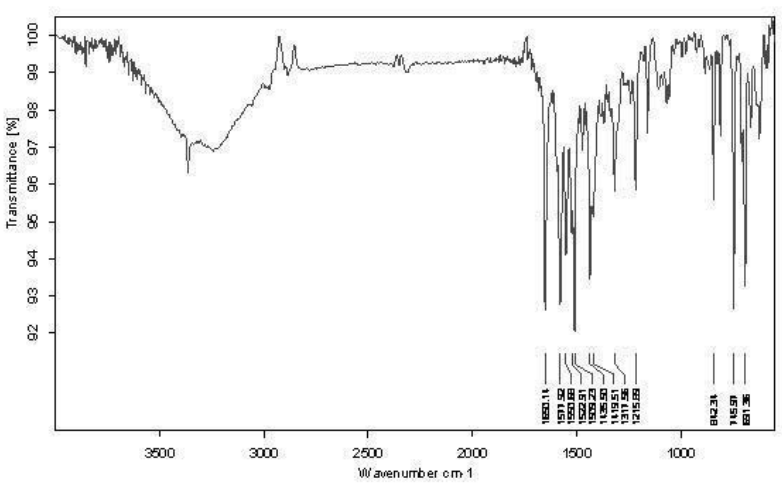


Fig 3: FTIR of pure drug

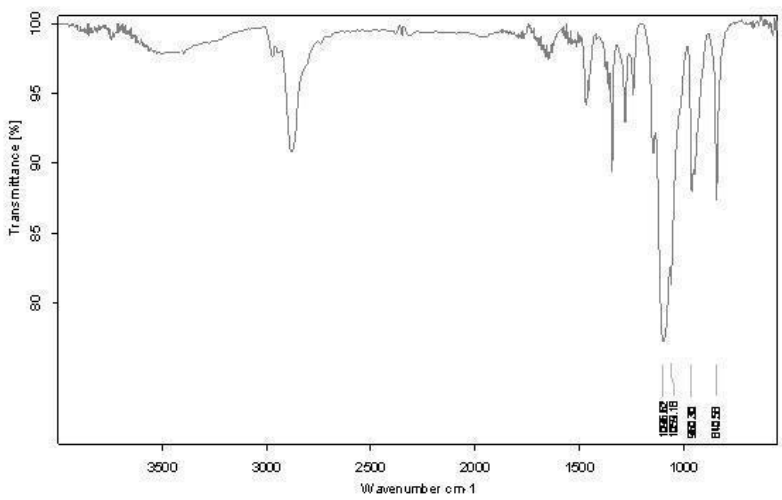


Fig 4: FTIR of Poloxamer 407 (polymer)

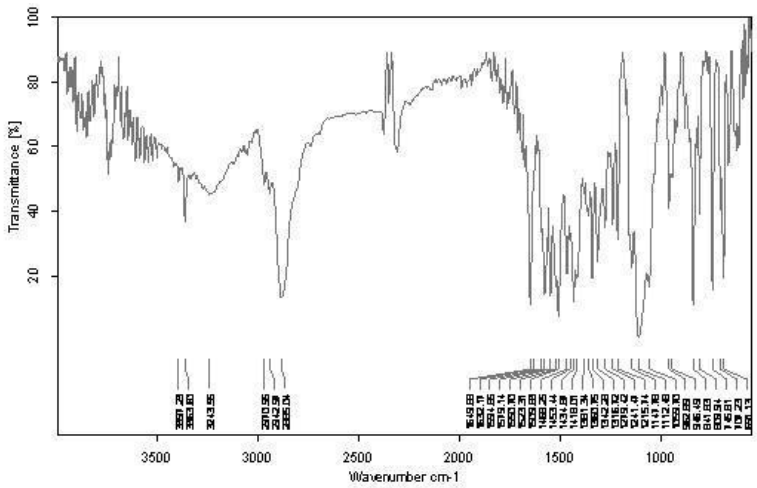


Fig 5: FTIR of physical mixture of pure drug and PXM 407 (1:2)

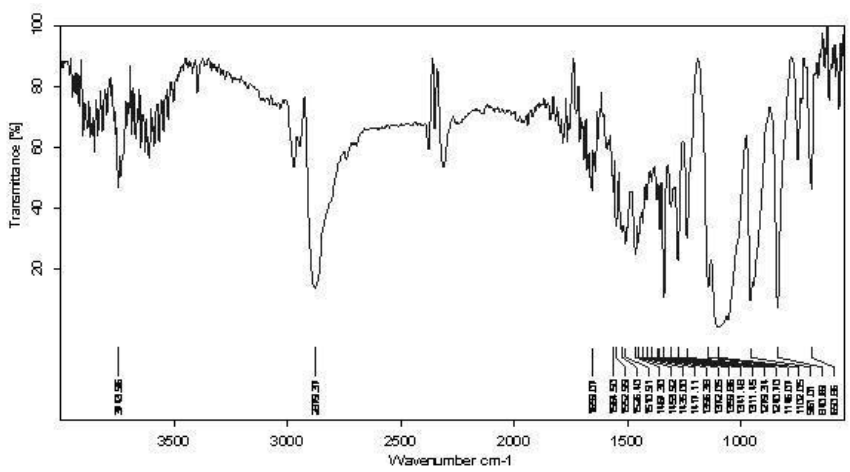


Fig 6: FTIR of Solid dispersion (PXM 407 1:2)

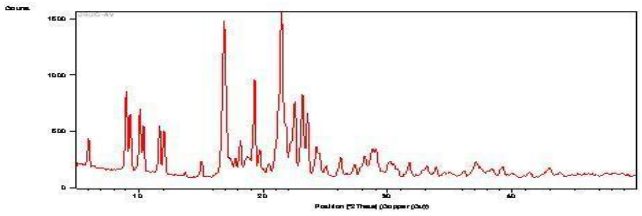


Fig 8 (a): XRD of Pure Drug

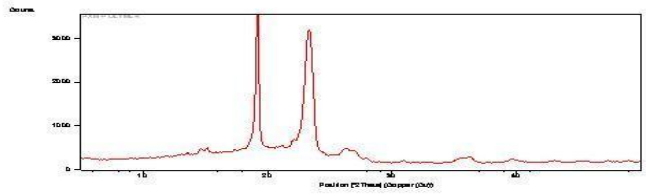


Fig 8 (b): XRD of PXM Polymer

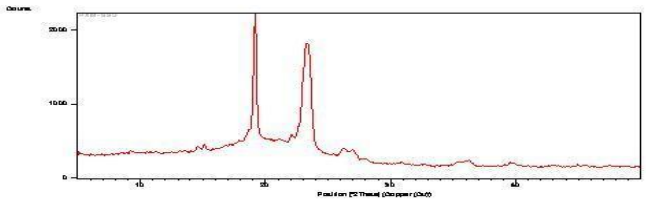


Fig 8 (c): XRD of PXM 407-Solid Dispersion (1:2)

Fig 9(a)

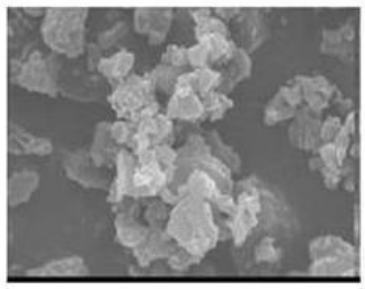


Fig 9(b)

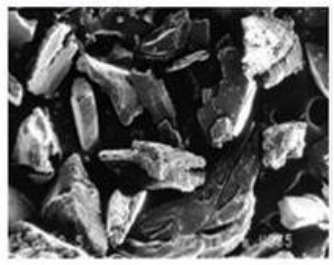
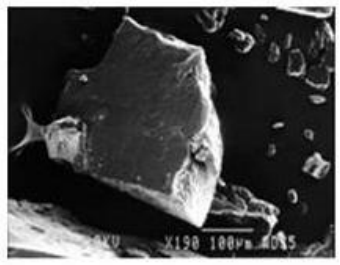


Fig 9(c)



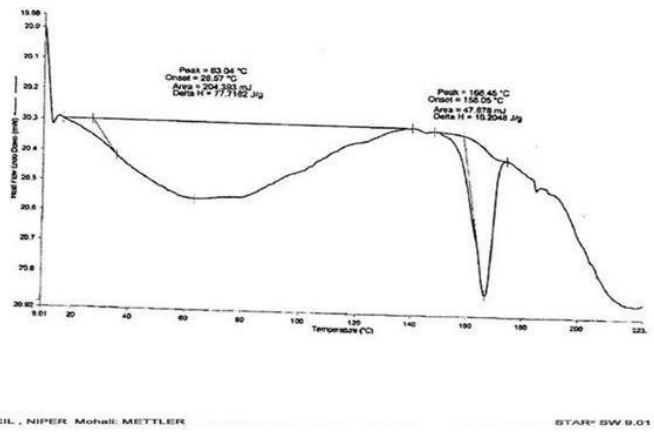


Fig 10: DSC thermogram of Atorvastatin calcium

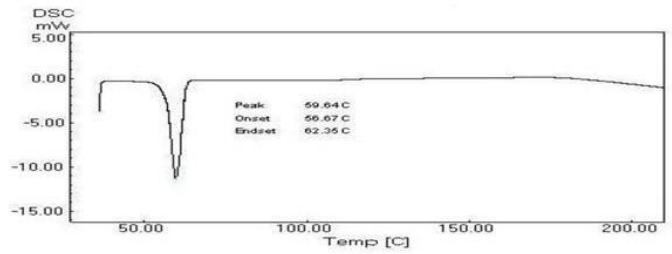


Fig 10 (a) DSC of PXM 407 polymer

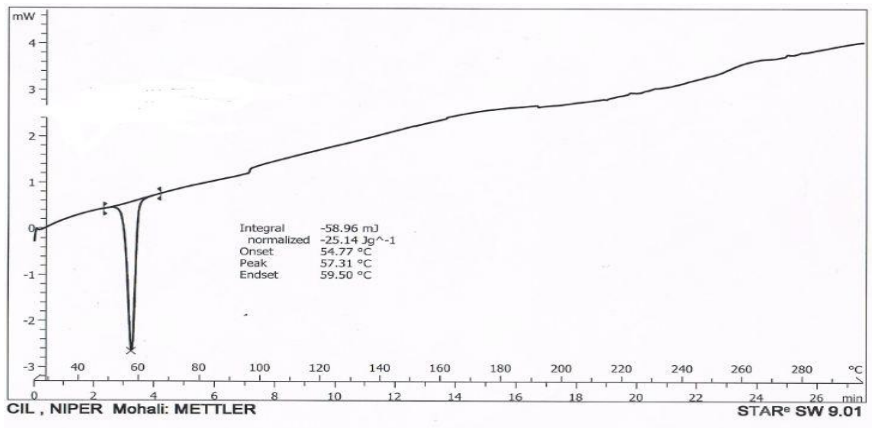


Fig 10(b): DSC of Solid dispersion.

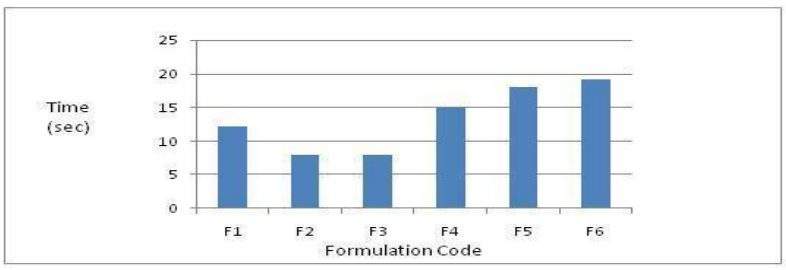


Fig 11: Dissolution profile of FDT formulation

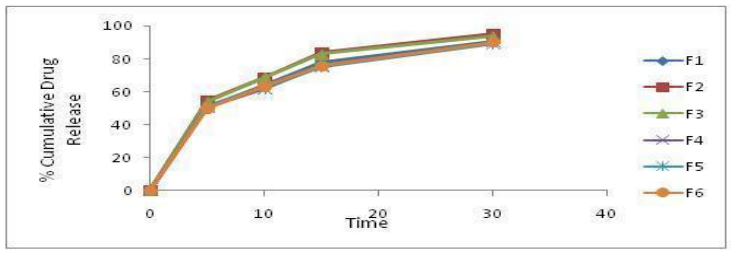


Fig 12: Disintegration time profile of FDT formulations

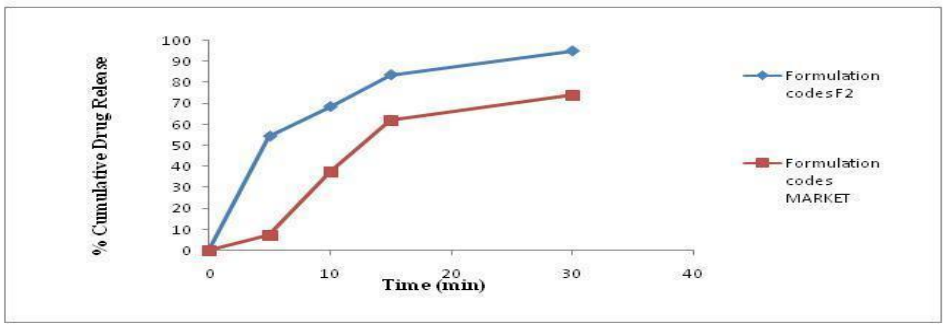


Fig 14: Comparative dissolution profile of best chosen formulation with market formulation

Table1. Description and code of solid dispersion formulations.

Formulation code	**Drug (mg)**	**Carrier (mg)**				**Drug and Carrier ratio**
0	ATV	PEG 4000	PEG6000	PVP K30	PXM 407	
S1	100 mg	100 mg	-	-	-	1:1
S2	100 mg	200 mg	-	-	-	1:2
S3	100 mg	300 mg	-	-	-	1:3
S4	100 mg	500 mg	-	-	-	1:5
S5	100 mg	-	100 mg	-	-	1:1
S6	100 mg	-	200 mg	-	-	1:2
S7	100 mg	-	300 mg	-	-	1:3
S8	100 mg	-	500 mg	-	-	1:5
S9	100 mg	-	-	100 mg	-	1:1
S10	100 mg	-	-	200 mg	-	1:2
S11	100 mg	-	-	300 mg	-	1:3
S12	100 mg	-	-	500 mg	-	1:5
S13	100 mg	-	-	-	100 mg	1:1
S14	100 mg	-	-	-	200 mg	1:2
S15	100 mg	-	-	-	300 mg	1:3
S16	100 mg	-	-	-	500 mg	1:5

Table 2: Description and code of FDT formulations of solid dispersed ATV.

Formulation Code	F1	F2	F3	F4	F5	F6
ATV (PXM 407) 1:2	30mg	30mg	30mg	30mg	30mg	30mg
MCC	60mg	60mg	60mg	60mg	60mg	60mg
Cross Povidone	7.5mg	10mg	12.5mg	-	-	-
Cross Carmellose	-	-	-	7.5mg	10mg	12.5mg
Mg-stearate	1.5mg	1.5mg	1.5mg	1.5mg	1.5mg	1.5mg
Talc	1.5mg	1.5mg	1.5mg	1.5mg	1.5mg	1.5mg
Mint flavour	1mg	1mg	1mg	1mg	1mg	1mg
Mannitol	48.5mg	46mg	43.5mg	48.5mg	46mg	43.5mg

Table 3: Standard graph data of Atorvastatin calcium.

S no.	Conc. (µg/ml)	Absorbance	± S.D.*
1	0	0.000	± 0.000
2	6	0.244	± 0.005
3	8	0.340	± 0.005
4	10	0.435	± 0.007
5	12	0.530	± 0.004
6	14	0.612	± 0.005
7	16	0.695	± 0.009
8	18	0.785	± 0.004
9	20	0.864	± 0.005

S.D.*= Average of three readings

Table 4: Solubility data of pure drug in phosphate buffer (pH 6.8).

S. No.	Solvent	Solubility(mg/ml ± SD)
1	Phosphate buffer (pH 6.8)	0.21±0.012

Table 5: Method of Preparation, Solubility Study, Percent Drug Content and Percent Drug Release of Solid Dispersions of Solid Dispersions.

Sr. no.	Carrier	Drug: Carrier ratio	Method of preparation	Solubility (mg/ml)		% Drug content	% Drug release
				Physical mixture	Solid dispersion		
1	PEG 4000	1:1	Fusion	0.26	0.32	91.2%	75.24%
2	PEG 4000	1:2	Fusion	0.24	0.29	90.3%	73.20%
3	PEG 4000	1:3	Fusion	0.24	0.21	90.2%	70.1%
4	PEG 4000	1:5	Fusion	0.23	0.28	89.6%	72.0%
5	PEG 6000	1:1	Fusion	0.25	0.30	96.5%	77.3%
6	PEG 6000	1:2	Fusion	0.23	0.28	94.3%	79.2%
7	PEG 6000	1:3	Fusion	0.27	0.32	98.2%	85.6%
8	PEG 6000	1:5	Fusion	0.24	0.29	97.1%	81.3%
9	PVP K30	1:1	S.E	0.25	0.31	96.2%	84.3%
10	PVP K30	1:2	S.E	0.28	0.35	98.4%	92.3%
11	PVP K30	1:3	S.E	0.26	0.32	94.6%	88.1%
12	PVP K30	1:5	S.E	0.26	0.30	96.3%	84.3%
13	PXM 407	1:1	S.E	0.25	0.32	95.5%	86.5%
14	PXM 407	1:2	S.E	0.30	0.39	99.0%	96.5%
15	PXM 407	1:3	S.E	0.27	0.35	97.4%	87.8%
16	PXM 407	1:5	S.E	0.28	0.33	96.2%	87.3%

S.E refers to Solvent Evaporation Method

Table 6: Dissolution data of pure drug and solid dispersions.

Time (Min)	Pure drug	PVP K30	PXM 407	PEG 4000	PEG 6000
0	0	0	0	0	0
5	17.93706	51.18653	58.02591	33.46632	43.41451
10	23.81119	61.60104	67.32009	43.08503	54.11578
15	27.58741	72.63731	78.19574	50.54082	62.19272
30	31.15385	81.34197	89.53685	59.0859	72.29186
45	35.97902	87.71503	93.10567	66.07597	78.6593
60	43.74126	92.37824	96.52338	75.24307	85.65058

Table 7: Physical Evaluation of ATV FDT.

Formulation Code	Avg. Wt of tablets(mg) ±S.D n=20	Hardness ±S.D n=5 (kg/cm^2)	Percentage Friability (%)	Disintegration Time (sec)	% Drug content
F1	156±0.04	3.97±0.17	0.54%±0.05	12±2.00	96.80%±0.21
F2	152±0.06	4.01±0.11	0.50%±0.03	8±2.00	97.36%±0.14
F3	154±0.10	4.04±0.21	0.62%±0.02	8±3.00	93.83%±0.19
F4	158±0.08	3.87±0.24	0.62%±0.04	15±1.00	94.00%±0.11
F5	153±0.12	3.93±0.22	0.64%±0.003	18±3.00	92.16%±0.15
F6	154±0.10	3.85±0.27	0.72%±0.01	20±2.00	93.80%±0.20

Table 8: Dissolution data of FDT formulations.

Time (min)	Formulation Code					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0
5	50.66 ± 0.43	54.44 ± 0.56	53.81 ± 1.19	50.66 ± 0.43	51.08 ± 0.39	50.03 ± 0.49
10	64.34 ± 0.37	68.49 ± 0.65	68.70 ± 0.29	61.99 ± 0.32	62.20 ± 0.28	63.25 ± 0.17
15	78.35 ± 0.64	83.60 ± 0.14	82.76 ± 0.24	75.83 ± 0.16	75.20 ± 0.97	75.62 ± 0.93
30	90.73 ± 0.27	94.93 ± 0.27	93.67 ± 0.33	90.10 ± 0.49	89.05 ± 0.59	89.89 ± 0.51

Table 9: Dissolution data of best chosen formulation with market formulation.

Time	Formulation	Code
	F2	**MARKET**
0	0	0
5	54.44 ± 0.56	07.23 ± 0.77
10	68.49 ± 0.65	37.44 ± 0.75
15	83.60 ± 0.14	61.99 ± 0.30
30	94.93 ± 0.27	73.95 ± 0.20

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