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Solubility Enhancement of Atorvast at in Calcium by Solid Dispersion Technique

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ABSTRACT
Hyperlipidemia is the presence of elevated abnormal levels of lipids or lipoproteins in the blood. Hyperlipidemia is regarded as a highly modifiable risk factor for cardiovascular diseases common in elderly patients. The Atorvastatin belongs to BCS class II drug having low solubility and high permeability. In the present study attempt was made to improve solubility and dissolution rate of poorly soluble drug by solid dispersion technique using carrier poloxamer 188. The FDA approved atorvastatin in December 1996. Atorvastatin, a synthetic lipid-lowering agent, is an inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase which catalyzes the conversion of HMG-CoA to mevalonate, an early rate-limiting step in cholesterol biosynthesis. Orally administered Atorvastatin calcium shows low bioavailability due to its low solubility in aqueous and acidic media. The objective of present study was to formulate and optimize solid dispersion tablet containing Atrovastatin calcium to improved solubility. The phase solubility study was adopted for the selection of carriers. Phase solubility revealed that the poloxamer188 was sufficiently able to enhance the aqueous solubility of Atrovastatin calcium. The solid dispersions were prepared by Solvent Evaporation method in different ratios viz. 1:1, 1:1.5, 1:2, 1:2.5, 1:3 & 1:3.5. The prepared solid dispersions were evaluated for physical appearance, solubility study, drug content, and in-vitro dissolution study. Thus the solid dispersion of Atorvastatin calcium tablets, comparable with the innovator formulation developed which could overcome the problem of low solubility. In-vitro dissolution solid dispersion tablet data revealed that ATRP4 batch of formulation was optimum due to its better drug release (94.26% at 30 minutes) even after solid dispersion. Tablets of optimized ATP4 batch were kept for stability study at 30 0 C ± 2 0 C/65%RH ± 5% RH and 40 0 C ± 2 0 C/75%RH ± 5% RH. Solid dispersion of Atorvastatin calcium tablets, comparable with the innovator formulation, was successfully developed which could overcome the problem of low solubility and instability in acidic environment.

Keywords: Atorvastatin calcium, solid dispersion, solvent evaporation method, aqueous solubility, dissolution rate.

I. INTRODUCTION:

Hyperlipidemia is also known as hyperlipoproteinemia because these fatty substances travel in the blood attached to proteins. This is the only way that these fatty substances can remain dissolved while in circulation. Other characteristics of lipoproteins are low density lipoprotein (LDL) and high density lipoprotein (HDL). Excess level of LDL indicates the blockage of arteries, which eventually leads to heart attack. In a Population studies have clearly shown that the greater the risk of heart disease(CVDs) is due to the higher the level of LDL cholesterol. As a result, LDL cholesterol referred to as a bad cholesterol. In contrast, the lower the level of HDL cholesterol, is lead to the greater the risk of coronary heart disease. Hence, HDL cholesterol has been labeled as the good cholesterol.

Cholesterol and other fatty substances combine in the bloodstream and are deposited in the blood vessels to form a material called plaque. The increase in lipids can cause plaques to grow over time, leading to obstructions in blood flow. If an obstruction occurs in the coronary arteries, it could result in a heart attack while an obstruction in the arteries of the brain, could lead to stroke.

The BCS was first contrived in 1995 by Amidon et al. since then it has become a benchmark in the regulation of bioavailability and bioequivalence of oral drug formulation. The characteristic of various BCS classes aids as a guiding tool to improving the efficacy of drug development by proper selection of dosage form and bioequivalence tests, to recommend a class of immediate release (IR) drug products.

Solubility Based Classification Of Drugs As Per United State Pharmacopeia (USP). USP & National formulary lists the solubility of a drug as the number of millilitres of solvents in which 1g of solute will

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dissolved. The concept of solid dispersion was originally proposed by Sekiguchi & obi, The term solid dispersion is defined as a group of solid products consisting of at least two different components, generally a hydrophilic matrix & a hydrophobic drugs. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particle (clusters) or in crystalline particle.

In the solvent evaporation method, solid dispersion is obtained after the evaporation of solvent from the solution containing a drug and carrier. Some polymers hardly used as carriers in the melting method due to their high melting point can be applied in the solvent method. An important prerequisite of this method is the sufficient solubility of the drug and carrier in a solvent or cosolvent. Finding a suitable non-toxic solvent is sometimes difficult because carriers are hydrophilic whereas drugs are hydrophobic. The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented, because of the relatively low temperatures required for the evaporation of organic solvents.

II. MATERIALS AND METHODS

Materials:

Atorvastatin calcium was purchased from Psychotropic India Limited, IP-2, Haridwar, Uttrakhand. Poloxamer was obtained as a gift sample from Ranbaxy Research and development Center Gurgaon, Haryana & other excipient such as Microcrystalline cellulose, Starch Sodium starch glycolate, Magnesium stearate, & Talc are used.

Methods:

Innovator Tablet Drug Release Profile in 40mg IR tablet

Media and dissolution condition:- The in-vitro release of Innovator IR 40mg tablets was carried out for 30min in pH 6.8 phosphate buffer. The studies were performed in USP dissolution apparatus II at 37 ± 0.5° C, 75 rpm speed and 900ml volume. Samples were taken at 5min, 10min, 15min, 20min, 25min and 30min and diluted to suitable concentration and analyzed for API content at 246.0 nm by using UV–visible spectrophotometer.

Time(min)	Cumulative%drugrelease
0	0
5	25.32
10	43.71
15	61.20
20	73.80
25	86.90
30	95.65

Table1Time point innovator's release profile

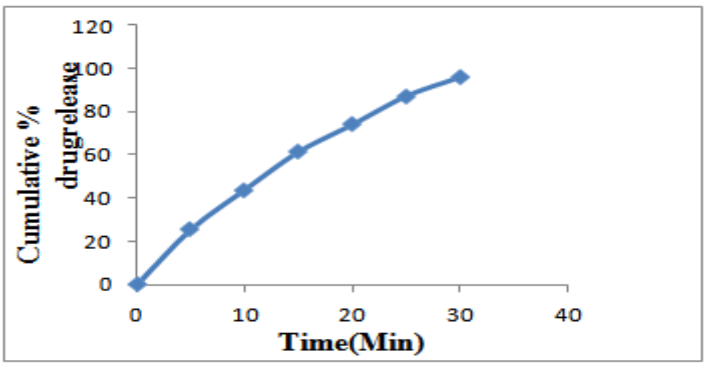

Figure1 Innovator's drug release profile

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Determination of λ_{max}

(a) Procedure

Atorvastatin calcium was dissolved in pH 6.8 Phosphate buffer. The solution was scanned for maximumabsorbance in UV double beam spectrophotometer [Shimandzu] in the range from 200 to 400 nm, using the respective solution as a blank. The λ_{max} of the API was 246.00 nm.

Standard Curve of Atorvastatin calcium

Preparation of solution to calibration curve- UV absorption shows lambda max to be 246.00 nm. The standard plot was prepared in methanol. From the standard stock solution (100µg/ml) take 0.5ml, 1.0ml, 1.5ml, 2.0ml, 2.5ml in 10ml volumetric flask & volume made upto the mark to obtained dilution of concentration 5µg/ml to 25µg/ml. Then absorbance was taken & calibration curve was plotted.

Preformulation Studies of Atorvastatin calcium

In physical characterization drug's physical state and solubility was measured.

Melting Point Determination

The melting point of a compound is the temperature at which it changes from a solid to liquid. Melting Pointof the drug sample was determined by using melting point apparatus. A capillary tube was taken and one endwas blocked by melting. Asmall amount of compound was placed on a clean surface. The compound wasput into the open end of the capillary tube. The capillary tube was placed into the melting point apparatus.Thesample was observed continuously forliquefaction and the meltingpoint was recorded.

Solubility study of Atorvastatin calcium: Solubility study was performed in Distilled water; 0.1N HCL, Methanol,Ethanol, pH 6.8 Phosphate buffer and Acetonitrile.

Compatibility Screening of drug with Excipients

For formulation development compatibility study between drug and excipients is necessary for stable dosageform on basis of its physical, chemical and biological characteristics. Drug-excipients interaction study wascarried out by taking 1:1 ratio (w/w) of drug and excipients in 2ml glass vials, sealed and placed in stabilitychamber at 25°C/60% RH, 40°C /75 % RH and 60°C for 21 days. The sample was analysed for any changes in colour and odourafter7, 15, &21 days.

Infrared studies:

Characterization FTIR studies- The IR studies were carried out by thepressed pellet technique using aKBr press in which the KBr was taken and kept in a hot air oven for two hours for the removal any moisture.The above dried KBr was taken for the preparation of pellets of drug, and the selected formulations. Theprepared pellet was placed in the sample holder and kept in the instrument to record the IR peaks. The resultsofthe infrared studies forthe selected batch arerecorded.

Preparation of batches Solid Dispersion

Atorvastatin calcium solid dispersion can be formed by using the drug & polymer at different ratio in thepresent study solid dispersion of atorvastatin calcium can be formed by using poloxamer 188 by different ratio respectively.

Table2 Composition of batches solid dispersion

Sr.No.	Formulation	Drug(mg)	Carrier(mg)
1	**ATRP1**	1	1
2	**ATRP2**	1	1.5
3	**ATRP3**	1	2
4	**ATRP4**	1	2.5
5	**ATRP5**	1	3
6	**ATRP6**	1	3.5

Preparation of solid dispersion of Atorvastatin calcium (ATR)

Solid dispersion of ATR in Poloxamer 188 was prepared in different ratios by solvent evaporation method.The Drug and carrier were dissolved in minimum volume of methanol &

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solvent was removed under vaccumin rotavapor at 40ºC & 45rpm for 24hrs. The resultant solid dispersion was kept in refrigerator for 2days toharden. Dispersion were then pulverlized in mortor& pestle, passed through a 250-µm sieve (mesh size 60),thenstored in a desiccator at room temperature.

Solubility studies of solid dispersion of ATR

Solubility may be defined as the amount of a substance that dissolves in a given volume of solvent at a specified temperature. Solubility measurements of Atorvastatin calcium were performed according to a published method by Higuchi & Connors. The amount of SD powder (mg) was weighed accurately in screw cap vials was dissolved 5ml methanol by sonication for 15 minute subsequently, the solutions were filtered through a whatman filter paper no 1. Filtered solution was diluted properly with methanol. The diluted solution was analyzed for the Atorvastatin calcium in UV at 246nm.

In vitro Dissolution study of solid dispersion

The dissolution rate of Atorvastatin calcium as such and from solid dispersions prepared was studied respectively in 900 ml of phosphate buffer pH 6.8 using USP type II (paddle type) dissolution test apparatus with a paddle stirrer at 75 rpm. A temperature 37±5ºC was maintained throughout the study. Drug or solid dispersion equivalent to 40 mg of Atorvastatin calcium was used in each test. Samples of dissolution media (5ml) were withdrawn through a filter (0.45µ) at different intervals of time, suitably diluted and assayed at 246 nm. The samples of dissolution fluid withdrawn at each time were replaced with fresh fluid.

Drug content Analysis of solid dispersion

Solid dispersions equivalent to 10 mg of Atorvastatin calcium were weighed accurately & dissolved in the 10ml of methanol & volume was made upto 50 ml. From this 1ml of solution was taken and further diluted 10times with methanol. The solution was filtered, diluted suitably and drug content was analyzed at 246 nm byUVspectrophotometer.Theactual drug contentwas calculated usingthefollowingequation as follows:

$$\%\text{Drug content} = (M_{act}/M_t) \times 100 \qquad (.\ 1)$$

Mact = Actual amount of drug in Solid dispersion

Mt = Theoretical amount of drug in solid dispersion

Evaluation of tablets

Physical Description: Tablets from all the batches & innovator were visually examined.

Diameter and Thickness

Diameter and thickness of tablets from all batches and innovator were measured by placing tablet between claws of digital calliper.

Average Weight and Weight Variation Test

Twenty tablets from each batch were weighed individually and the average weight was calculated. From average and individual weight, percentage weight variation was calculated.

Hardness Test

Hardness of tablet was determined using Monsanto hardness tester. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger was placed in contact with the tablet and a zero reading was taken. The upper plunger was then forced against a spring by turning a threaded bolt until the tablet was fractured. As the spring was compressed, pointer ridded along a gauge in the barrel to indicate the force.

Friability Test

Friability was determined by taking thirty six tablets (pre-weighed) equivalent to 6.5g from each batch and placing them in a Roche Friabilator operated at 25 rpm for 4 minutes. Tablets were then dusted, reweighed and percentage friability was calculated.

$$\%\text{Friability} = (\text{Wt. initial} - \text{Wt. final} / \text{Wt. initial}) \times 100 \qquad (....2)$$

Disintegration Test

The disintegration apparatus consist of basket of six tubes with a base of metal sieve of 10 mesh. Thisassembly was suspended using a hanger with a mechanism of vertical motion at fixed speed of 28-32cycles/minute in the phosphate buffer pH 6.8 maintained at 37 ± 2^0C. The time required for disintegration oftabletwas recorded.

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Stability testing of API

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug productvaries with time under the influence of a variety of environmental factors such as temperature, humidity, andlight,andto establisha re-testperiodfor the drugsubstance or a shelf life for the drugproductandrecommended storage conditions.

Table3 Different storage conditions

Study	**Storagecondition**	**Minimumtimeperiod coveredby dataatsubmission**
Longterm	25°C± 2°C/60%RH ±5%RH	12months
Intermediate	30°C± 2°C/65%RH ±5%RH	6months
Accelerated	40°C± 2°C/75%RH ±5%RH	6months

III. RESULT & DISCUSSION

Method of analysis of Atorvastatin Calcium

The absorbance was measured in a UV spectrophotometer at 246nm in Distilled water, pH 6.8 phosphate buffer, Methanol, Ethanol, 0.1N HCl and Acetonitrile. The scan observed in Methanol.

Concentration(µg/ml)	**Absorbance**			**AverageAbsorbance**
	1	2	3	
5	0.175	0.173	0.174	0.174
10	0.331	0.344	0.33	0.335
15	0.491	0.495	0.494	0.493
20	0.652	0.66	0.663	0.658
25	0.804	0.804	0.803	0.804
LinearEquation		y=0.0322x +0.0085		
R^2value		R^2 =0.9995		
Slope(m)		0.0322x		
Intercept(c)		0.0085		

Table4 Standard curve data of Atorvastatin Calcium in methanol

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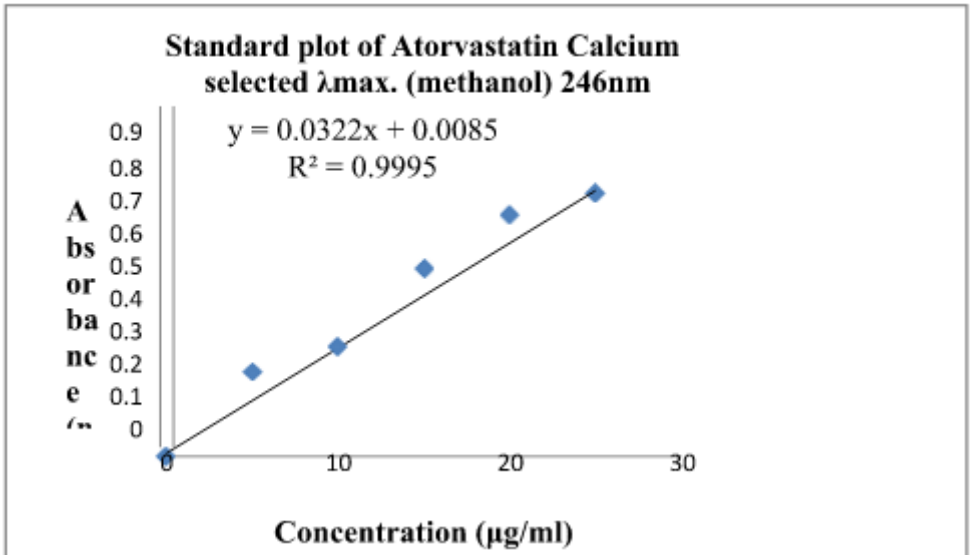

Fig 2: Standard Plot of Atorvastatin Calcium in Methanol

Preformulation Studies of Atorvastatin calcium

Physical appearance: A white to off-white, crystalline powder without any characteristic odour.

Melting Point Determination

The actual melting point of Atorvastatin calcium was determined by capillary method & it was found to be157.7^{0}C.This was agood agreement with the actual meltingrange.

Compatibility Screeningof drug with Excipients

Various excipients were selected according to their function from the compatibility study report and based on review of literature and their concentration in formulation was optimized by taking different trial batches. No significant change was observed during compatibility studies of API and excipients at all the three conditions

Table5 Condition-25ºC ±2ºC /60%RH ± 5%RH

S.No.	Ingredients	Initial	1st Week	2nd Week	3rd Week
1	ATR	Whitepowder	NC	NC	NC
2	ATR+POLOXAMER 188	Whitepowder	NC	NC	NC
3	ATR+MCC	Whitepowder	NC	NC	NC
4	ATR+STARCH	Whitepowder	NC	NC	NC
5	ATR+SSG	Whitepowder	NC	NC	NC
6	ATR+TALC	Whitepowder	NC	NC	NC
7	ATR+Mag.Stearate	Whitepowder	NC	NC	NC

Table6 Condition-40ºC ±2ºC/ 75% RH± 5%RH

S.No.	Ingredients	Initial	1st Week	2nd Week	3rd Week
1	ATR	Whitepowder	NC	NC	NC
2	ATR+POLOXAMER188	Whitepowder	NC	NC	NC

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3	**ATR+MCC**	Whitepowder	NC	NC	NC
4	**ATR+STARCH**	Whitepowder	NC	NC	NC
5	**ATR+SSG**	Whitepowder	NC	NC	NC
6	**ATR+TALC**	Whitepowder	NC	NC	NC
7	**ATR+Mag. Stearate**	Whitepowder	NC	NC	NC

Table7 Condition-60ºC ±2ºC

S.No.	Ingredients	Initial	1st Week	2nd Week	3rd Week
1	**ATR**	Whitepowder	NC	NC	NC
2	**ATR+POLOXAMER188**	Whitepowder	NC	NC	NC
3	**ATR+MCC**	Whitepowder	NC	NC	NC
4	**ATR+STARCH**	Whitepowder	NC	NC	NC
5	**ATR+SSG**	Whitepowder	NC	NC	NC
6	**ATR+TALC**	Whitepowder	NC	NC	NC
7	**ATR+Mag. Stearate**	Whitepowder	NC	NC	NC

Where ATR (Atorvastatin calcium IP), ** (same as initial), NC (No change)

Results of FT-IR spectrum interpretation

The IR spectrum of ATR is shown in figure 6.4. The IR spectrum showed various characteristic peaks. All observed peaks justifies the presence of all functional groups present ATR.

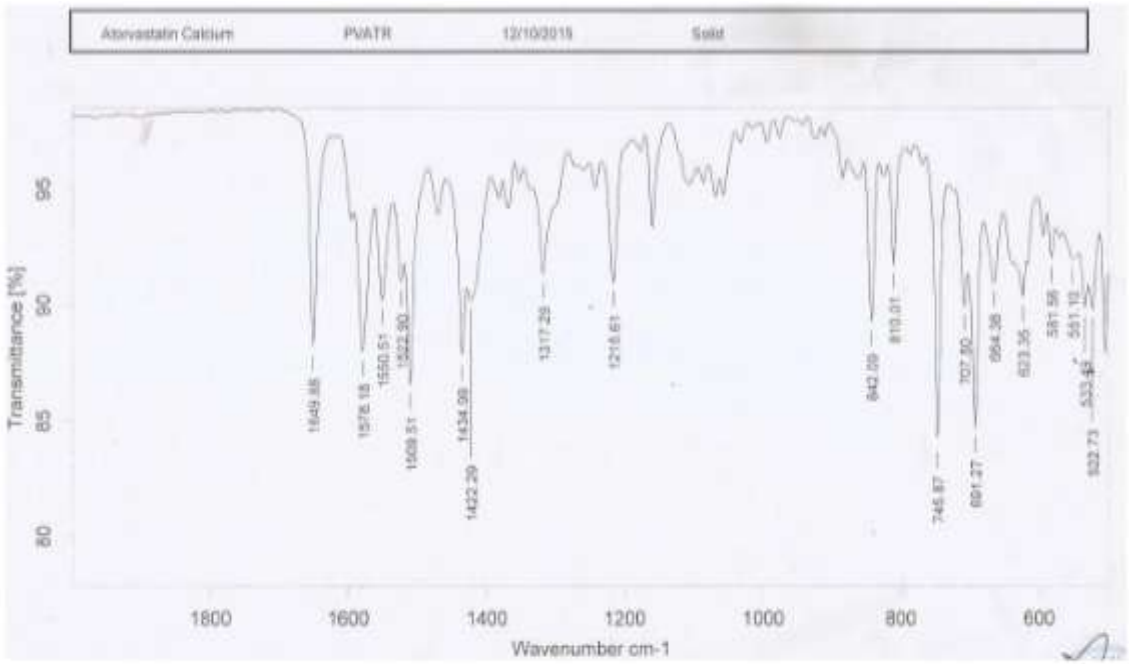

Fig. 3 FT-IR spectra of Atorvastatin calcium

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Table8 FT-IR peaks and functional category

Peaks(cm^{-1})	Functional groups
1435	-CH_2 bending
1216	C-Ostretching
1650	C=Ostretching
1578	N-Hbending
1510	C=Cstretchingin aromatic
1317	C-Nstretching

The infrared spectrophotometer a study was carried out for the API and optimized batch for extended release tablet. The IR data and IR spectrum for the API excipients and tablet are indicated in Figure 6.8 respectively. The FTIR data for the API indicated that the functional group's peaks indicated in spectra are identical with the theoretical peaks, so this indicates the purity of the API. The peaks of all the functional groups in FT-IR spectra of optimized formulation are identical with that of the pure drug XYZ. From the IR studies it was found that there was no interaction of the drug-excipient and excipient-excipient because there is no change in functional groups peak. So, all the excipients are compatible with API.

Solubility study of solid dispersion of Atorvastatin calcium

Solubility of all solid dispersion can be increased as compared to pure drug by solid dispersion increasing the concentration of polymer. The formulation ATRP4 showed the more solubility than pure drug (ATR).

Sr. No.	Formulation	Drug	Solubility µg/ml
1	ATR	Pure drug	2.05
2	ATRP1	1:1	9.16
3	ATRP2	1:1.5	13.22
4	ATRP3	1:2	19.34
5	ATRP4	1:2.5	23.09
6	ATRP5	1:3	16.24
7	ATRP6	1:3.5	12.19

Table 9 Solubility study of solid dispersion

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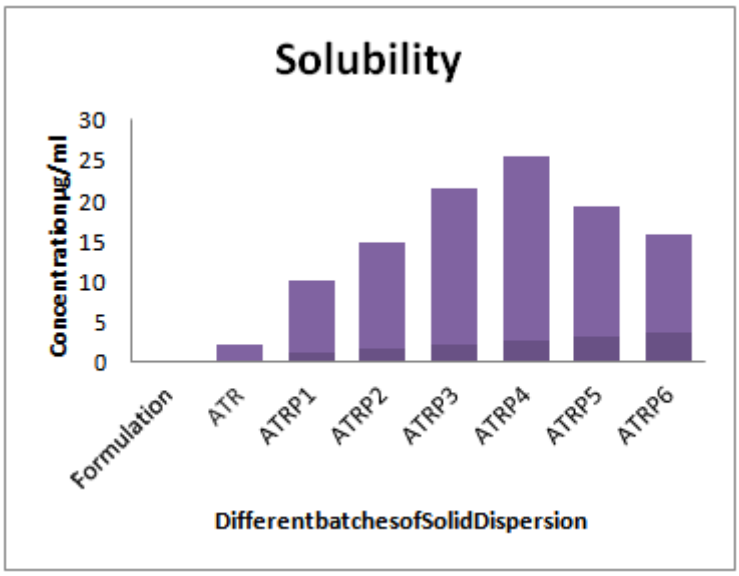

Fig 4 Solubility study of solid dispersion.

In-vitro Dissolution Study of Solid Dispersion

The dissolution profile of the solid dispersion was shown in figure 6.6. The dissolution rate of Atorvastatin calcium solid dispersion was higher for all the formulation when compared with pure drug (ATR).

Table10 In-vitro dissolution data of solid dispersion

Time(min.)	Innovatorproduct (Atorvastatin40 mg)	ATRP1	ATRP2	ATRP3	ATRP4	ATRP5	ATRP6
00.00	**00.00**	**00.00**	**00.00**	**00.00**	**00.00**	**00.00**	**00.00**
5	**25.32**	24.77	25.08	25.10	**27.6**	26.9	27.4
10	**43.71**	41.1	40.2	39.89	**41.6**	41.26	39.6
15	**61.20**	60.11	61.3	59.36	**60.4**	61.2	59.20
20	**73.80**	74.3	72.24	75.45	**74.7**	72.7	74.2
25	**86.90**	82.25	83.5	82.6	**85.3**	82.55	81.5
30	**95.65**	91.35	92.83	91.10	**93.58**	91.24	91.5

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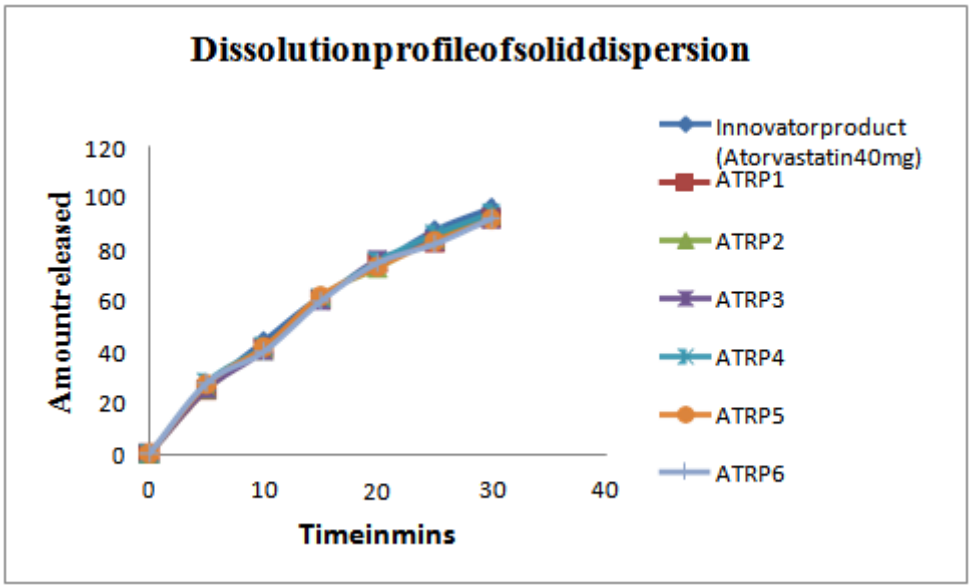

Fig5 Dissolution study of solid dispersion

Drug Content Analysis

Table11Drug content analysis of solid dispersion

S.no	Formulation code	Drug: Carrier	%Drug Content
1	**ATRP1**	1:1	91.27
2	**ATRP2**	1:1.5	92.34
3	**ATRP3**	1:2	91.99
4	**ATRP4**	1:2.5	94.28
5	**ATRP5**	1:3	93.84
6	**ATRP6**	1:3.5	90.21

Formulation of Tablet from Solid Dispersion

Table 12 Formula for tablet(mg)

Ingredients	ATRP1	ATRP2	ATRP3	ATRP4	ATRP5	ATRP6
AtorvastatinCaIP	40	40	40	40	40	40
MCCIP	49	47	45	51	53	55
StarchIP	62	64	66	60	58	56
SSGIP	25	25	25	25	25	25
MgstearateIP	1.5	1.5	1.5	1.5	1.5	1.5
TalcumIP	2.5	2.5	2.5	2.5	2.5	2.5
Totalweight(mg)	180	180	180	180	180	180

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Where- SSG is sodium starch glycolate and MCC is microcrystalline cellulose.

Rheological properties

Table 13 Flow Properties of granules

Parameters	**ATRP1**	**ATRP2**	**ATRP3**	**ATRP4**	**ATRP5**	**ATRP6**
Angleofrepose(degrees)	34.29	32.76	32.48	**32.68**	31.21	32.41
Bulk density(g/ml)	0.563	0.612	0.569	**0.626**	0.591	0.643
Tapped density(g/ml)	0.746	0.820	0.754	**0.830**	0.766	0.846
%Compressibilityindex	24.53	25.37	24.54	**24.58**	22.85	23.40
Hausnerratio	1.33	1.34	1.32	**1.33**	1.30	1.32

Evaluation of tablets:

All the formulations showed values within the prescribed limits for tests like hardness, friability, weight variation, disintegration time and drug release which indicate that the prepared tablets are of standard quality. Here Innovator product is Atorvastatin 40 mg is used.

Table14Evaluation of tablet of Atorvastatin calcium solid dispersion

Batch	**ATRP1**	**ATRP2**	**ATRP3**	**ATRP4**	**ATR5**	**ATRP6**	**Innovator**
Diameter(mm) (8.0 ± 0.2)	8.01±0.06	7.98±0.09	8.00±0.06	7.96±0.05	7.98±0.06	7.99±0.09	8.00±0.10
Thickness(mm) (3.5 ± 0.3)	3.27±0.03	3.30±0.03	3.27±0.01	3.29±0.06	3.28±0.03	3.28±0.01	3.28±0.04
Averageweight (mg)	180.42	180.15	180.74	180.51	181.14	181.02	180.12
%Weightvariation(within±7.5 % of Av.Wt.)	-3.16to +4.12	-2.58to +3.41	-3.15to+4.34	-2.48to+2.05	-3.15to +4.34	-4.19to +3.40	-2.01to +2.00
Hardness(kg/cm^2)	2.63±0.17	3.68±0.21	3.53±0.13	3.25±0.07	4.12±0.17	3.69±0.06	3.26±0.24
Friability(%) (NMT1.0%)	0.31	0.16	0.10	0.15	0.04	0.16	0.09
Disintegration time (min)(NMT15min)	6.25	13.40	12.21	7.15	14.50	9:34	7.13

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The shape of the tablets of all formulations remained circular & biconvex with no visible cracks, capping or lamination. The disintegration time of all batches remained within the range of 6.25minutes to 14.50minutes which is within Pharmacopoeial limit. The diameter, thickness, average percentage weight variation, hardness, percentage friability, disintegration time and drug release within 30minutes of innovator product (Atorvastatin 40mg) were found to be 8.00±0.10mm, 3.28±0.04mm, within ±5%, 3.26±0.24kg/cm 2 , 0.09%, 7:13minutes and 95.65% respectively.

In-Vitro Dissolution Studies of tablets

Table 15 In-vitro dissolution data (cumulative %drug release) of tablets

Time(min.)	Innovatorproduct(Atorvastatin 40mg)	ATRP1	ATRP2	ATRP3	ATRP4	ATRP5	ATRP6
00.00	**00.00**	**00.00**	**00.00**	**00.00**	**00.00**	**00.00**	**00.00**
5	**25.32**	26.77	25.12	26.30	**27.6**	26.9	27.4
10	**43.71**	42.1	40.4	40.05	**41.6**	41.26	44.6
15	**61.20**	60.11	61.3	59.36	**60.4**	61.2	60.21
20	**73.80**	75.3	77.3	76.45	**74.7**	75.7	74.2
25	**86.90**	85.25	86.6	87.6	**85.3**	85.55	84.5
30	**95.65**	92.49	93.84	92.10	**94.26**	91.62	92.3

The ATRP4 was optimized on the basis of resemblance with innovator (Atorvastatin 40mg) in terms of betterdrug release profile, disintegration time, hardness, dissolution and friability of drug as compared to other formulation batches. The result was found to be satisfactory as innovator product (Atorvastatin 40mg).

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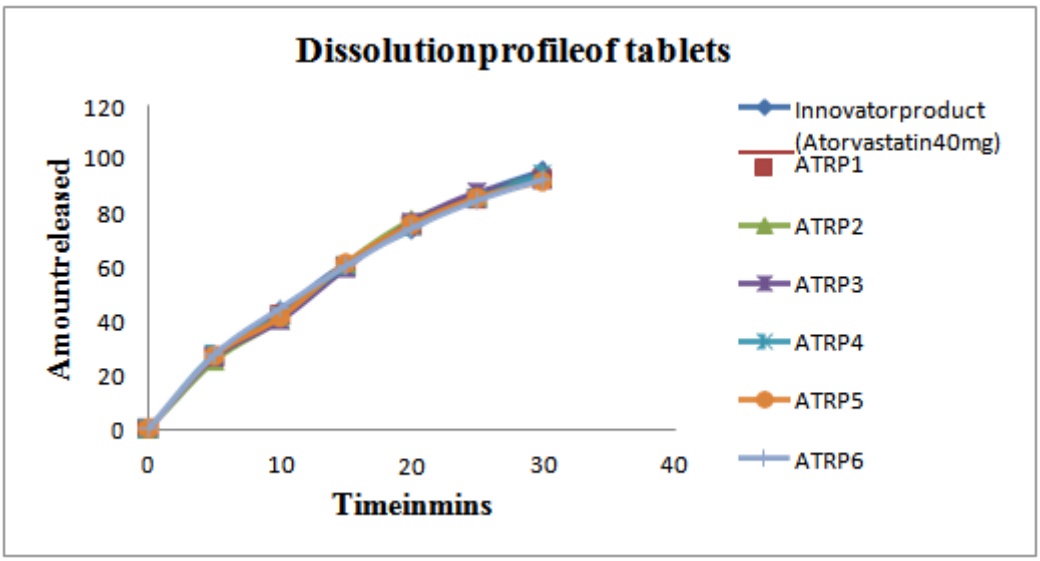

Fig 6 In-Vitro Dissolution Studies from tablets

Table16 In-vitro dissolution data of ATRP 4& innovator

Dissolutiontime(minutes)	CumulativeDrugrelease(%)	
	ATRP4	Innovator(Atorvastatin40mg)
0	0	0
5	27.6	25.32
10	41.6	43.71
15	60.4	61.20
20	74.7	73.80
25	85.3	86.90
30	94.26	95.65

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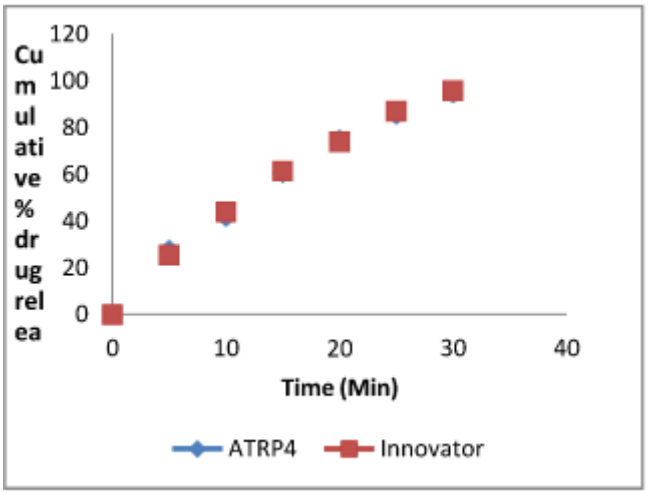

Fig. 7 Comparative dissolution profile of SD tablet of ATRP4 & innovator

Drug Release kinetic

The in-vitro release data obtained were fitted in to various kinetic equations (i.e. zero, first, higuchi, korsmeyer, hixson and peppas kinetic model) of the optimized formulation ATRP4 was following the higuchi more linearly than other models.

Table17Results of drug release kinetics using various models

Formulation Code	R^2Values				n-Value
	Zeroorder	firstorder	Higuchimodel	Korsmayer-peppas	
ATRP4	0.9641	0.9562	0.9817	0.9599	0.9927

Stability testing of Atorvastatin calcium (Optimized formulation) : The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions.

In general, a drug substance should be evaluated under storage conditions (with appropriate tolerances) that test its thermo stability and, if applicable, its sensitivity to moisture re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions.In general, a drug substance should be evaluated under storage conditions (with appropriate tolerances) thattest its thermo stabilityand, if applicable, its sensitivityto moisture

Table 18 Stability data of optimized batch ATRP4 at 30 0 C ± 2 0 C/65% RH ±5%RH

Testprotocol	Specification	Samplingtime(in months)			
		Initial	1 M	2 M	3 M
Description	Circular,biconvex	Complies	Complies	Complies	Complies

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Disintegration time(min.)	NMT30	7:31	6:50	7:20	7:18
%Drugrelease (in 30 min.)	NLT75%in45min.	93.81	94.26	92.67	91.79
Assay: AtorvastatinCaeq.toAtorvastatin 40 mg	38-42mg/tablet 90-110%	39.86 mg99.30%	39.80 mg99.00%	39.72 mg98.60%	39.60 mg98.00%

Table 19 Stability data of optimized batch ATRP4 at 40 0 C ± 2 0 C/75% RH± 5%RH

Testprotocol	**Specification**	**Samplingtime(in month)**			
		Initial	**1 M**	**2 M**	**3 M**
Description	Circular,biconvex	Complies	Complies	Complies	Complies
Disintegration time (min.)	NMT30	7:31	7:27	7:53	7:49
%Drugrelease(in 30 min.)	NLT85%in45 min.	93.81	92.26	90.94	89.79
Assay:AtorvastatinCaeq. to Atorvastatin40mg	38-42mg/tablet 90-110%	39.86 mg99.30%	39.77 mg98.85%	39.61 mg98.05%	39.43 mg97.15%

SHELF-LIFE AND ITS CALCULATION

Table 20 Shelf-life of optimized formulationATRP4

S.No.	**Parameters**	**Storageconditions**	
		30^0C/65%RH	**40^0C/75%RH**
1	K($days^{-1}$)	1.54×10^{-4}	2.303×10^{-4}
2	$t_{1/2}$(days)	4500	3009.12
3	$t_{0.9}$(days)	681.82	455.93

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Solid dispersion of Atorvastatin calcium tablets stored at 30 0 C ± 2 0 C/65% RH ± 5%RH showed K value as 1.54 x 10 -4 day -1 , t 0.9 value as 681.82 days and t 1/2 value as 4500 days, while those stored at 40 0 C ± 2 0 C/ 75% RH ± 5% RH showed K value as 2.303 x 10 -4 day -1 , t 0.9 value as 455.93 days and t 1/2 value as 3009.12 days.

The value of K obtained in case of Atorvastatin calcium tablets stored at 40^0C ± 2^0C/75% RH ± 5% RH wasfoundto be greaterthan thosestored at 30^0C ± 2^0C/65% RH ± 5% RH.

The results of stability studies suggest that for adequate shelf life of Atorvastatin calcium tablet, the ideal storage temperature is not to exceed 30 0 C and relative humidity not to exceed 65%.

IV. CONCLUSION

Atorvastatin calcium was identified & characterized as per requirements of official monograph. Melting point range was found to be in between 157.7 0 C, which is near to the official range 159.2-160.7 0 C as per literature. Atorvastatin calcium solid dispersions were prepared by solvent evaporation method. Solubility of all solid dispersion can be increased as compared to pure drug by solid dispersion increasing the concentration of polymer. The formulation ATRP4 (23.09 µg/ml) showed the more solubility than pure drug (2.05 µg/ml). Drug content of all solid dispersion is acceptable range. The dissolution rate of Atorvastatin calcium solid dispersion was higher for all the formulation when compared with pure drug. It was concluded that there was no significant change in the formulated tablets even after solid dispersion. Thus the solid dispersion of Atorvastatin calcium tablets, comparable with the innovator formulation (Atorvastatin 40mg), was successfully developed which could overcome the problem of low solubility. Tablets of optimized ATP4 batch were kept for stability study at 30 0 C ± 2 0 C/65%RH ± 5% RH and 40 0 C ± 2 0 C/75%RH ± 5% RH and it was found that the drug degradation rate constant at 40 0 C ± 2 0 C/75% RH ± 5% RH was greater than those stored at 30 0 C ± 2 0 C/65% RH ± 5% RH. Finally it was concluded that for better stability Atorvastatin calcium tablet should be stored at a temperature and RH not exceeding 30 0 C and 65% respectively.

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