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Polymer Based Formulation Strategies for Immediate Release Atorvastatin Calcium Tablets: An Evaluation Study

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ABSTRACT

Atorvastatin calcium, a potent HMG-CoA reductase inhibitor, exhibits limited oral bioavailability (~14%) due to poor water solubility. This study aimed to enhance its solubility and dissolution characteristics through solid dispersion techniques using hydrophilic polymers PEG 6000 and β-cyclodextrin and subsequent formulation of immediate-release tablets. Solid dispersions were prepared using direct compression, and eight formulations (F1–F8) were developed with varying polymer ratios. Preformulation studies, UV calibration, and physicochemical characterization were conducted. The optimized formulation F6 exhibited significantly improved dissolution profiles, suggesting solid dispersion as a viable approach to enhance the bioavailability of poorly water-soluble drugs like Atorvastatin Calcium.

KEY WORDS: Atorvastatin calcium, solid dispersion, PEG 6000, β-cyclodextrin, immediate-release tablets, polymer-based formulation, bioavailability enhancement.

INTRODUCTION

Oral drug delivery remains the most preferred route due to convenience, cost-effectiveness, and patient compliance (Lachman et al., 1990). However, many drugs belong to the Biopharmaceutics Classification System (BCS) Class II category, characterized by low solubility and high permeability, which hinders their oral bioavailability (Debnath & Kumar, 2013).

Rahan, R., & Islam, M. S. (2013) studied about Atorvastatin binary solid dispersion. It deals with improvement in the solubility and dissolution rate. In this, solubility of Atorvastatin was increased by using hydrophilic carrier poloxamer. Physical mixing and solvent evaporation method were used to prepare ATV-SD where different drug carrier ratios were used. Prepared formulations were characterised in their solid state by solubility study; differential scanning colorimetry, scanning electron microscopy, and Fourier transform infrared spectroscopy which demonstrated changes in the formulations supporting the improved solubility. In case physical mixing, highest enhancement in drug release was found for 1:3 ratio where as in case of solvent evaporation, 3:0.5 ratio show enhancement in drug release.

Monika Sharma et al., (2013), designed Atorvastatin calcium solid dispersion to increase its solubility and there by its bioavailability. It is prepared by using PEG 4000 was as a carrier, in different ratios by conventional fusion and microwave induced fusion method. In particular, the microwave technology has been considered in order to prepare an enhanced release dosage form for poorly water-soluble drug ATC. Their physicochemical characteristics and dissolution properties were compared to the corresponding dispersions and pure drug. Three different formulations were prepared using conventional fusion method and microwave induced fusion method in different ratios i.e., 1:1, 1:2, 1:3 and 1:1, 1:2, 1:3 respectively, were further characterised by FTIR, DSC and SEM analysis. The results of FTIR revealed that no chemical interaction between the drug and the polymer exist. DSC studies showed that the drug as in amorphous state completely entrapped by the polymer. SEM studies showed the surface morphology of the solid dispersion. All the formulations showed a marked increase in drug release with the increase in the concentration of PEG-4000 when tested for their in-vitro studies. Formulation T5 showed the best release with a

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cumulative release of 86.15% in 0 minutes, when compared to pure drug and marketed formulation (Dhirendra, K., & Lewis, S. 2009).

Atorvastatin calcium is a widely used lipid-lowering agent that competitively inhibits HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis. Despite its efficacy, the drug's aqueous solubility is very low, resulting in only about 14% oral bioavailability (Sharma & Garg, 2013). Thus, enhancing the solubility of atorvastatin calcium is crucial for maximizing its therapeutic potential.

Solid dispersion is a promising technique to improve the dissolution rate and bioavailability of poorly soluble drugs by dispersing them into hydrophilic carriers like PEG 6000 and β-cyclodextrin (Agarwal, 2012; Modi & Tayade, 2006). These polymers enhance wettability, reduce crystallinity, and improve surface area of the drug, leading to faster dissolution (Chivate & Patil, 2012).

Therefore, the present study focuses on formulating immediate-release tablets of atorvastatin calcium using solid dispersion strategies with PEG 6000 and β-cyclodextrin, and evaluating their *in vitro* performance.

MATERIALS AND METHODS

Materials

Atorvastatin calcium was procured from Rainbow Labs, Hyderabad. PEG 6000 and β-cyclodextrin were obtained from Loba Chemie Pvt. Ltd. All other excipients were of analytical grade and used as received.

Methods

Solid dispersions were prepared by direct compression. The drug was uniformly mixed with PEG 6000 and β-cyclodextrin in different ratios. All ingredients were passed through sieve no. 80 to ensure uniformity and then blended thoroughly. The mixtures were directly compressed into tablets using a Cadmach single punch machine. The formulations were evaluated for various pharmacopoeial parameters including hardness, friability, disintegration time, and drug release profiles using phosphate buffer (pH 6.8).

Table 1: Formulation Composition

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
API (ATC)	40	40	40	40	40	40	40	40
Lactose	40	40	40	40	40	40	40	40
MCC	256	248	248	216	196	176	216	136
Calcium Carbonate	12	12	12	12	12	12	12	12
HPMC	20	20	20	20	20	20	20	20
PEG 6000	0	8	8	0	0	40	0	120
β-cyclodextrin	0	0	0	40	60	40	40	0
Talc	4	4	4	4	4	4	4	4
Croscarmellose sodium	24	24	24	24	24	24	24	24
Magnesium stearate	4	4	4	4	4	4	4	4

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1. Calibration Curve of Atorvastatin Calcium

Preparation of pH 6.8 Phosphate Buffer

To prepare 1000 mL of phosphate buffer (pH 6.8), Dissolve 28.80 g of Disodium Hydrogen Phosphate (Na_2HPO_4) and 11.45 g of potassium dihydrogen phosphate (KH_2PO_4) in sufficient distilled water and make up the volume to 1000 mL.

Procedure for Calibration Curve

An accurately weighed 10 mg of Atorvastatin calcium was dissolved in 10 mL of pH 6.8 buffer to obtain a stock solution of 1000 µg/mL.

From this stock solution: 1 mL was pipetted into a 10 mL volumetric flask and diluted up to the mark with buffer to obtain a 100 µg/mL solution. From this, 1 mL was further diluted to 10 mL to yield a 10 µg/mL solution.

The 10 µg/mL solution was scanned over the range of 200–400 nm using a double beam UV-visible spectrophotometer, with pH 6.8 buffer as the blank. The wavelength of maximum absorbance (λmax) was determined and recorded as the characteristic λmax of Atorvastatin calcium.

Preparation of Standard Calibration Curve

From the **stock solution (1000 µg/mL)**: Aliquots of 0.5, 0.75, 1.0, 1.25, and 1.5 mL were pipetted into separate 10 mL volumetric flasks. Each flask was made up to the mark with pH 6.8 buffer to yield concentrations of 50, 75, 100, 125, and 150 µg/mL, respectively.

The absorbance of each dilution was measured at 246 nm (λmax), and a standard calibration curve of concentration vs. absorbance was plotted.

2. Preformulation Studies

Preformulation studies are the initial step in the rational development of pharmaceutical dosage forms. These studies involve a thorough investigation of the physical and chemical properties of the drug substance, both alone and in combination with various excipients.

3. Pre-Compression Parameters

Before tablet compression, the powder blends of various formulations were evaluated for their flow and packing characteristics. The following parameters were studied:

I. Angle of Repose (θ)

The angle of repose is a measure of the frictional forces between particles. It is defined as the maximum angle formed between the surface of a pile of powder and the horizontal plane. A lower angle indicates better flow properties, while a higher angle suggests poor flow.

It is calculated using the formula:

$$\tan \theta = h/r$$
$$\theta = \tan^{-1} (h/r)$$

Where, θ = angle of repose; h = height of the pile; r = radius of the base

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The granules were allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

II. Bulk density

Bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder was determined.

Bulk density=Mass of powder/Volume of packing

III. Tapped density

The measuring cylinder containing a known mass of powder blend was tapped for a fixed number of times as per USP apparatus-11. The minimum volume occupied by the powder after tapping was measured.

Tapped density = Mass of powder/Tapped volume of packing

IV. Compressibility index or Carr's index: Compressibility index is calculated as follows

Carr's index = Tapped density- Bulk density/ Tapped density x 100

Grading of the powders for their flow properties according to Carr's index:

V. Hausner's ratio:

It is an indirect index of ease of powder flow, it is calculated as follows.

Hausner's ratio = Tapped density/Bulk density

Hausner's ratio <1.25 indicates good flow properties, whereas>1.5 indicates poor flowability.

Compatibility studies

The compatibility of drug and polymer under experimental condition is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymer and excipients under experimental condition and after the shelf life of the product.

This is confirmed by Infrared light scanning spectroscopy. It is most powerful technique for chemical identification of the drug.

Evaluation of Tablets

The formulated **Atorvastatin calcium solid dispersion tablets** were subjected to various quality control tests to assess their physical, chemical, and *in vitro* performance characteristics, as per standard pharmacopeial procedures.

I. Weight Variation Test

Twenty tablets were randomly selected from each batch. The average weight was calculated, and each tablet was weighed individually. The deviation from the mean was determined and compared against pharmacopeial limits.

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Table 2: Permissible Limits for Weight Variation:

Average Weight of Tablet	Permitted Percentage Deviation
130 mg or less	±10%
More than 130 mg and < 324 mg	±7.5%
324 mg or more	±5%

II. Hardness Test

Tablet hardness is indicative of its mechanical strength and ability to withstand handling, packaging, and transportation. It was measured using a **Pfizer hardness tester** and expressed in **kg/cm²**. Three tablets were randomly selected from each batch and tested.

III. Friability Test

Friability measures the tablet's resistance to abrasion and surface damage during handling. The test was conducted using a **Roche friabilator**.

Procedure:
- Weigh six tablets (Initial weight).
- Rotate the friabilator at 25 rpm for 4 minutes (100 revolutions).
- Reweigh the tablets (Final weight).

Friability (%) was calculated as:

$$\text{Friability (\%)} = W_{initial} - W_{final} / W_{initial} \times 100$$

Tablets with **friability < 1%** are considered acceptable.

IV. Thickness

Three tablets from each formulation were selected at random, and the thickness was measured using a dial calliper. The values were expressed in millimetres (mm), and the mean ± standard deviation was calculated.

V. Drug Content Uniformity

Drug content was determined to ensure uniform distribution of Atorvastatin calcium in the tablets. Tablets equivalent to 10 mg of drug were powdered and dissolved in 100 mL of phosphate buffer (pH 6.8). The solution was filtered, and 1 mL of the filtrate was further diluted to 10 mL with the same buffer. The absorbance was measured at 246 nm using a UV spectrophotometer, and the concentration was determined from the standard calibration curve.

VI. *In vitro* Disintegration Time

Disintegration time refers to the time taken for a tablet to break down into smaller fragments under physiological conditions. Six tablets were placed in individual tubes of a disintegration test apparatus. A disc was added to each tube, and the apparatus was operated in pH 6.8 buffer (simulated saliva fluid) at 37±2°C. The basket assembly was raised and lowered at 30 cycles per minute. The time taken for complete disintegration of each tablet with no visible residue was recorded.

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VII. *In vitro* Dispersion Time

The dispersion time is defined as the time required for a tablet to disperse completely in a liquid medium. One tablet was placed in a beaker containing 6 mL of pH 6.8 buffer. Three tablets per batch were tested, and the average dispersion time was recorded.

VIII. In-vitro Dissolution Studies

The dissolution profile of the tablets was evaluated using the USP Type II (paddle) **apparatus** to determine the rate and extent of drug release.

Table 3: Dissolution Test Parameters

Parameter	Condition
Dissolution Medium	900 mL of phosphate buffer (pH 6.8)
Temperature	37 ± 1°C
Rotation Speed (RPM)	50 rpm
Tablet per test	1 tablet
Volume withdrawn	5 mL
Wavelength (λ_{max})	246 nm
Sampling Intervals	5, 10, 15, 20, 30, 45 minutes

After each withdrawal, the medium was replaced with an equal volume of fresh buffer to maintain sink conditions. The samples were analysed spectrophotometrically at 246 nm, and the cumulative percentage of drug release was calculated and plotted against time.

RESULTS AND DISCUSSION

The solid dispersions of Atorvastatin calcium were successfully formulated using PEG 6000 and β-cyclodextrin as hydrophilic carriers. Eight formulations (F1–F8) were developed using direct compression technique and evaluated for physical and dissolution characteristics.

Table 4: Standard calibration curve of Atorvastatin calcium

Concentration (µg/ml)	Absorbance
0	0
50	0.1868
75	0.2782
100	0.3673
125	0.4564

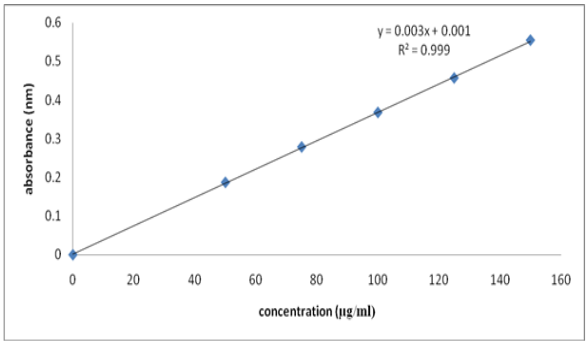

Figure 1: Calibration Curve of Atorvastatin Calcium

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2. Compatibility Studies

Fourier Transform Infrared Spectroscopy (FTIR) was employed to assess any potential interactions between Atorvastatin calcium and the excipients used in the formulation. The spectra obtained for the pure drug and the formulated solid dispersions are presented in Figures 2 and 3. There were no significant shifts, disappearance, or formation of new peaks, which suggests that no chemical interaction occurred between the drug and the polymers during the formulation process.

The FTIR spectra confirm that Atorvastatin calcium is chemically compatible with the selected excipients, and the drug remains stable and intact in the solid dispersion formulations.

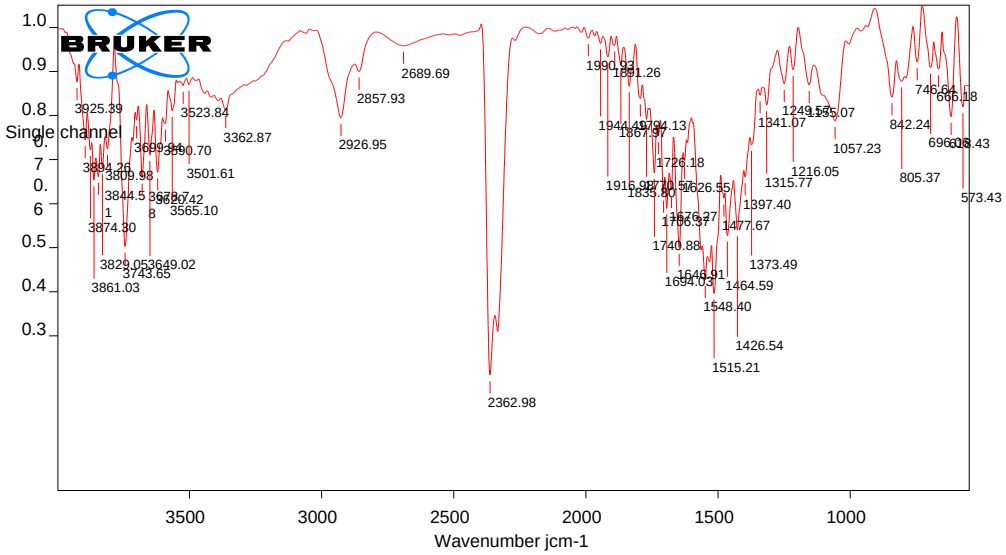

Figure 2: FTIR of pure drug Atorvastatin calcium

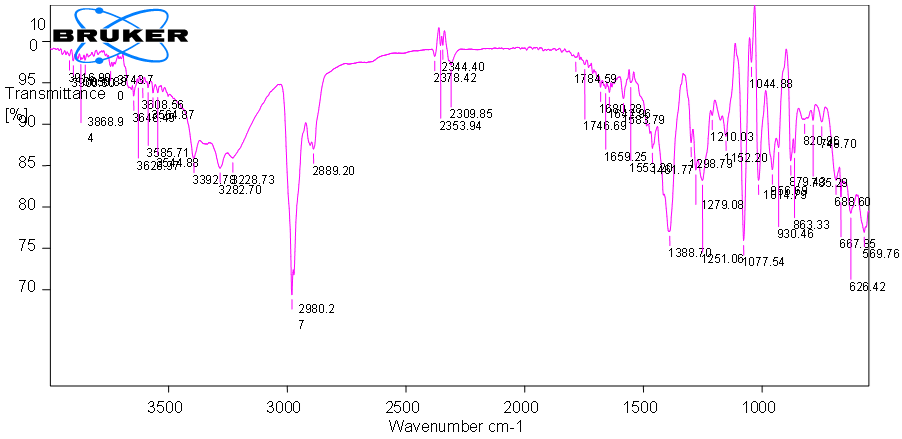

Figure 3: FTIR of optimized formulation

3. Melting point determination

The melting point of Atorvastatin calcium was found to be 158.2°C, which compiled with pharmacopeia standards thus indicating purity of obtained drug sample.

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4. Pre-Compression Parameters

The flow properties of the formulations were found to be in limit and the optimized formula was in limit and has a fair flowing property. This had no effect during compression of tablet.

Table 5: Results of Preformulation studies

Formulation code	B.D(gm/cm^3)	T.D (gm/cm^3)	C.I (%)	H. R	Angle of repose
F1	0.61	0.71	13.24	1.16	29.13
F2	0.62	0.71	13.33	1.14	27.32
F3	0.60	0.73	16.68	1.21	29.53
F4	0.61	0.72	15.28	1.18	28.13
F5	0.59	0.69	14.49	1.16	30.01
F6	0.60	0.71	15.49	1.18	29.13
F7	0.62	0.75	17.33	1.20	30.17
F8	0.62	0.73	16.43	1.17	28.63

5. EVALUATION OF TABLETS

Table 6: Results of evaluation parameters

S. No	Physical parameter	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8
1	Weight variation (%)	1.65	1.57	1.42	1.54	1.18	1.35	1.44	1.28
2	Hardness (kg/cm^2)	5.8	5.6	5.3	4.5	5.52	5.25	5.31	4.42
3	Thickness (mm)	2.1	2.11	2.15	2.2	2.13	2.16	2.19	2.2
4	Friability %	0.45	0.52	0.21	0.18	0.38	0.57	0.46	0.48
5	Disintegration time	1min 46 sec	1min 52 sec	2min 32 sec	2min 22 sec	1min 44 sec	1min 08 sec	1min 50 sec	1min 48 sec

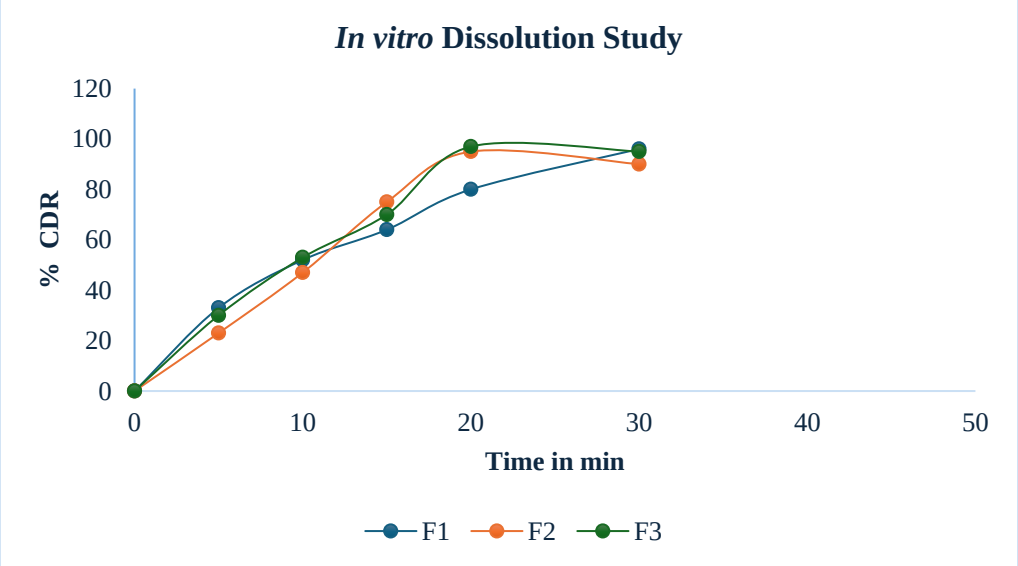

Figure 4: Comparison of *in-vitro* drug release studies for F1-F3 formulations

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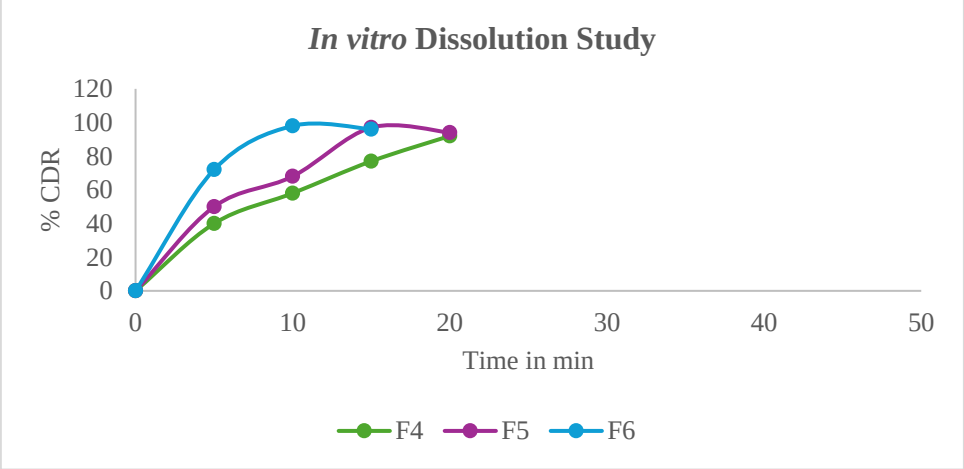

Figure 5: Comparison of in-vitro drug release studies for F4-F6 formulations

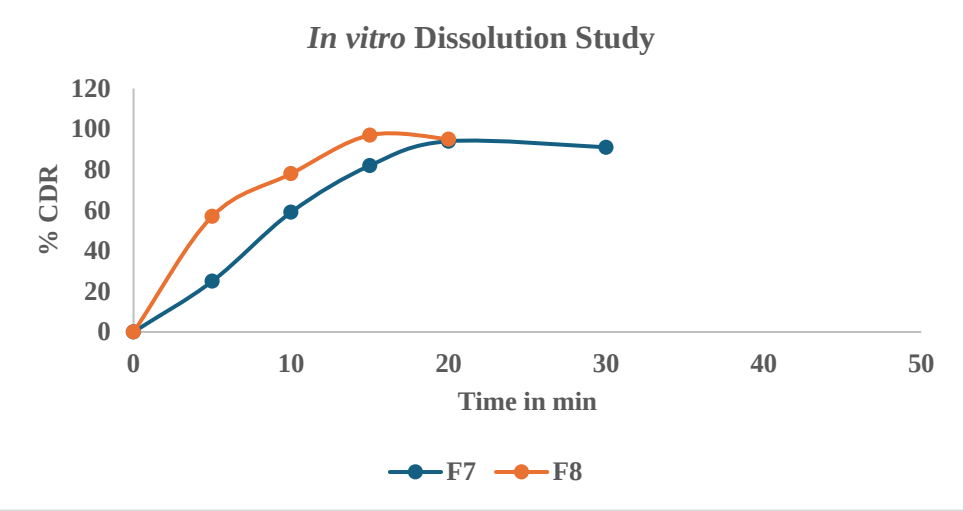

Figure 6: Comparison of *in vitro* drug release studies for F7-F8 formulations

Formulation F6 emerged as the optimal formulation, showing superior dissolution characteristics, indicating its potential for enhanced bioavailability of Atorvastatin calcium in immediate-release tablet form.

Drug content

Table 7: Results of drug content

Formulation code	Drug content
F1	95.3
F2	93.7
F3	97.8
F4	94.6
F5	97.9
F6	98.2
F7	96.8
F8	96.7

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The drug content in the solid dispersions was almost same and the assay was in the range and the assay did not drop in the solid dispersion the value was above 90%.

8. Stability Studies

To provide documented evidence that the formulated Atorvastatin calcium tablets (Formulation F6) remain compliant with specified physical, chemical, and performance parameters under both accelerated and long-term storage conditions.

Dissolution Profile of Formulation F6

Table 8: Dissolution at 25°C / 60% RH (After 1 Month)

Time (min)	% Drug Release (Initial)	% Drug Release (After 1 Month)
0	0	0
5	72	72
10	98	96

Table 9: Dissolution at 40°C / 75% RH (After 1 Month)

Time (min)	% Drug Release (Initial)	% Drug Release (After 1 Month)
0	0	0
5	72	73
10	98	97

The results of the stability studies indicate that no significant changes were observed in the physical characteristics (appearance, weight, hardness, thickness, and friability) of the Atorvastatin calcium tablets (**Formulation F6**) after storage for one month under both accelerated (40°C / 75% RH) and long-term (25°C / 60% RH) conditions.

Similarly, the *in vitro* dissolution profiles showed negligible variation, confirming that the drug release characteristics remain stable under the tested conditions.

CONCLUSION

This study demonstrates that the solid dispersion technique using hydrophilic polymers like PEG 6000 and β-cyclodextrin effectively enhances the dissolution rate of atorvastatin calcium. Formulations F6 excellent drug release, highlighting the importance of optimized polymer ratios. Solid dispersion through direct compression is a simple yet robust approach to improve the solubility and bioavailability of poorly water-soluble drugs such as atorvastatin calcium.

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