



CODEN [USA]: IAJPB

ISSN : 2349-7750

**INDO AMERICAN JOURNAL OF  
PHARMACEUTICAL SCIENCES**

SJIF Impact Factor: 7.187

<https://doi.org/10.5281/zenodo.6102350>Available online at: <http://www.iajps.com>

Research Article

**ENHANCEMENT OF SOLUBILITY AND  
DEVELOPMENT OF FAST DISSOLVING ORAL FILM  
OF ATORVASTATIN**<sup>1</sup>Vinod Kumar, <sup>2</sup>Anwar Iqbal Khan, <sup>3</sup>Dr Navjot Singh<sup>1</sup>NRI Institute of Pharmacy, Bhopal M.P.

Article Received: January 2022

Accepted: January 2022

Published: February 2022

**Abstract:**

Fast dissolving oral film are those when put on tongue disintegrate/dissolve/disperse instantaneously releasing the drug which dissolve or disperses in the saliva with Their characteristic advantages such as administration without water, anywhere, anytime lead to their suitability to geriatric and paediatric patients. Atorvastatin is prescribed to treatment of hypertension. Therefore, a new Atorvastatin calcium preparation that is useful for swallow function deficient patients is needed. Keeping an objective an attempt is made to develop fast dissolving oral film of Atorvastatin. The preliminary study showed that Atorvastatin is White to off-white and Odorless powder. It is freely soluble in methanol and ethanol and soluble in 0.1 N Hydrochloric acids, Phosphate buffer pH 6.8, and slightly soluble in water the melting point was in the range of 158-160 °C which is compliance with the standard value of as per Indian Pharmacopoeia. Identification of Atorvastatin was performed by UV/VIS Spectroscopy. The  $\lambda_{max}$  of Atorvastatin was found to be 248nm. From the respective stock solution (1mg/ml) different concentration of 5, 10, 15, 20 and 25 $\mu$ g/ml Atorvastatin was prepared and scanned in UV region. Fast dissolving oral film oral film containing Atorvastatin were prepared using solvent casting method. The prepared Oral film was further evaluated for disintegration time, and uniformity of drug content, and In- vitro Release Studies. Percentage assay of different formulation was determined by U.V. vis Spectroscopy. The percentage assay of different formulation was in range of 95.23 $\pm$ 0.65 to 99.56 $\pm$ 0.58%. The maximum percentage assay (99.56 $\pm$ 0.58%) and less disintegration time were found in formulation F6 in fast dissolving oral film. The optimized formulation of batch F6 subjected to further In vitro drug release.

Keywords: Optimization, Dosage form, Drug, Evaluation, Release

**Corresponding author:****Vinod Kumar**

NRI Institute of Pharmacy, Bhopal M.P.

QR code



Please cite this article in press Vinod Kumar al, *Enhancement Of Solubility And Development Of Fast Dissolving Oral Film Of Atorvastatin.*, Indo Am. J. P. Sci, 2022; 09(2).

**INTRODUCTION:**

Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous system and is one of the important parameters to achieve desired concentration of drug in systemic circulation for pharmacological response. Poorly water-soluble drugs after oral administration often require high doses in order to reach therapeutic plasma concentrations. The bioavailability of an orally administered drug depends on its solubility in aqueous media over different pH ranges. The insufficient dissolution rate of the drug is the limiting factor in the oral bioavailability of poorly water-soluble compounds. Various techniques are used for the improvement of the aqueous solubility, dissolution rate, and bioavailability of poorly water-soluble drugs include micronization, chemical modification, pH adjustment, solid dispersion, complexation, cosolvency, micellar solubilization, hydrotrophy etc. Throughout the past decade, in the development and commercialization of new pharmaceutical products, the formulation and

delivery of Active Pharmaceutical Ingredients (APIs) have played a crucial role. To improve bioavailability, stability and convenience to the patient, is the major objective of formulation chemistry (Majerik *et al.*, 2004). Bioavailability means the rate and extent to which the active substance or therapeutic moiety is absorbed from a pharmaceutical form and becomes available at the site of action (Vemavarapu *et al.*, 2005). The bioavailability of an orally administered drug depends on its solubility in aqueous media over the pH range of 1.0–7.5 and the rate of mass transfer across biological membranes (Charbit *et al.*, 2004). In the oral bioavailability of poorly water soluble compounds, the insufficient dissolution rate is the limiting factor (Rogers *et al.*, 2001). Some new technologies have been recently developed to improve wettability and aqueous solubility of APIs. These methods are based on the use of compressed gases, supercritical fluids, and anti-solvent (Jung and Perrut, (2001).

**MATERIALS AND METHODS:****Table 1: List of drug and Excipients used**

Sr. No.	Chemicals	Supplier
1.	Atorvastatin	Gift sample from Bioplus life science, Bangalore
2.	PVP	S. D. Fine Chem. Ltd., Mumbai
3.	Citric acid	Qualigens fine chemicals, Mumbai
4.	HPMC	Ozone international, Mumbai
5.	Sodium bicarbonate	Chem pure Pvt. Ltd
6.	Magnesium stearate	Jiangsu Huaxi International
7.	Talc	Loba Chemie Pvt. Ltd Mumbai
8.	Lactose	Loba Chemie Pvt. Ltd Mumbai

**Table 2: List of instruments used**

Sr. No.	Instrument / Apparatus	Supplier
1.	UV -Visible Spectrophotometer	Labindia 3000+ Mumbai
2.	Fourier Transform Infra-Red Spectroscopy	Brucker, Alpha, Germany
3.	pH Meter	Electronic India
4.	Electronic Balance	Wensor, India
5.	Melting Point Apparatus	Chemline CL-725
6.	Hot Air Oven	Electronic India
7.	Sonicator	Electronic India
8.	Dissolution Testing Apparatus	Labindia DS- 8000 Mumbai
9.	Tablet compression machine	10 station compression machines

**METHODS:****Formulation development of oral film of Atorvastatin:****Casting process of fast disintegrating oral film:**

Various methods are available for casting of oral films. This is fast disintegrating oral film hence on the laboratory scale solvent casting technique was adopted for formulation of films.

**Solvent casting technique:**

Drug (Atorvastatin) containing fast dissolving films were fabricated by the solvent casting method. The optimized amount of HPMC was dissolved in 5ml of water and stirrer continuously for 1 hour, optimized amount of Plasticizer and drug were dissolved in 95% ethanol and then added to the polymeric solution, the optimized amount of drug was dissolved in 2ml of water and kept on sonication for proper dispersion. Polymeric solution was stirred for 30 min using magnetic stirrer and was kept in undisturbed condition

till the entrapped air bubbles were removed. The aqueous solution was casted in a glass moulds having 2.5 x 2.5 cm \* 10 films area and was dried at controlled room temperature (25°-30°C, 45 %RH) as well as at increased temperature (microwave oven). The film took approximately 48 hr to dry at controlled room temperature. The dried film was carefully removed from the glass plates and was cut into size required for testing. The films were stored in air tight plastic bags till further use.

**Selection and optimization of film forming agents:**

Two film forming agents and one co-film forming were selected for this research work. The concentration of film forming was important to form a proper thickness for appropriate packaging and handling of oral films. Concentration of film forming agent is optimized on the basis of thickness and appearance of film.

**Optimization of formulations****Table 3: Selection and Optimization of Film Forming Agents**

Name of ingredients (mg for 12 strips)	F1	F2	F3	F4	F5	F6
API Equivalent to 120 mg	240	240	240	240	240	240
HPMC	250	500	750	250	500	750
Glycerin	-	-	-	-	-	-
PEG-400	100	100	100	100	100	100
SSG	150	200	-	-	-	-
CCS	-	-	150	200	-	-
CP	-	-	-	-	150	200
Aspartame	50	50	50	50	50	50
Citric acid	100	100	100	100	100	100
DM water qs to (ml)	30	30	30	30	30	30

**Dose calculations**

- Width of the plate = 5cm
- Length of the plate = 12cm
- No. of 2.5 x 2.5 cm<sup>2</sup> films present whole plate = 12
- Each film contains 20 mg of drug.
- 12 no. of films contains mg of drug? = 10×12 = 120mg
- The amount of drug added in each plate was approximately equal to 120 mg.

**RESULT AND DISCUSSION:**

Results of Preformulation study

**Organoleptic evaluation**

Table No. 1: Organoleptic property of Atorvastatin

Drug	Atorvastatin
Color	White powder
Odor	Odorless

**Result:** It was found that Atorvastatin is white powder and Taste was bitter.  
**Solubility (at room temperature)**

Table No. 2: Solubility studies of Atorvastatin in different solvent

S. No.	Solvent Used	Atorvastatin
1.	Water	Slightly soluble
2.	0.1 N HCl	Soluble
3.	Ethanol	Freely Soluble
4.	Methanol	Freely Soluble
5.	Chloroform	Soluble
6.	0.1 N NaOH	Sparingly soluble
7.	Phosphate buffer pH 6.8	Sparingly Soluble

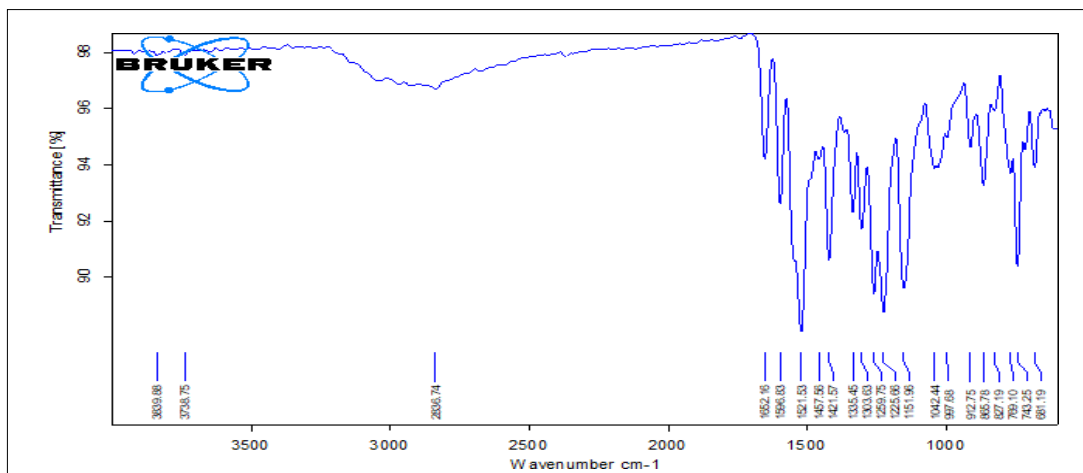
**RESULT:**

It was found that Atorvastatin was slightly soluble in water, freely soluble in ethanol and methanol, soluble in 0.1 N HCl and Chloroform, and sparingly soluble in 0.1 N NaOH and phosphate buffer pH 6.8.

**Identification Test**

FTIR Spectroscopy:

Figure 1: FT-IR Spectrum of Pure Drug (Atorvastatin)

**Loss on drying**

**Result of loss on drying:** The percentage of loss on drying of Atorvastatin was

1.482%.

**Melting point:**

**Result:** Melting point was determined by Melting point apparatus and found 158- 160 °C for Atorvastatin.

**Bulk Properties:****Table No. 3: Bulk density of Atorvastatin**

S. No.	Bulk mass	Bulk volume	Bulk density	Avg. Bulk density
1.	1 gm	1.9 ml	0.526 g/ml	0.526 g/ml
2.	1 gm	ml	0.555 g/ml	
3.	1 gm	ml	0.526 g/ml	

**Results:** Bulk density of Atorvastatin was **0.526** g/ml

**Result of Tapped density****Table No. 4: Tapped density of Atorvastatin**

S. No.	Bulk mass	Tapped volume	Tapped density	Avg. tapped density
1.	1 gm	1.5 ml	0.666 g/ ml	0.666 g/ ml
2.	1 gm	1.5 ml	0.666 g/ ml	
3.	1 gm	1.4 ml	0.714 g/ ml	

**Results:** Bulk density of Atorvastatin was **0.666** g/ml.

**Result of Compressibility index (Carr's index)****Table No. 5: C.I. of Atorvastatin**

S. No.	Bulk density	Tapped density	C.I.
1.	0.76 g/ml	0.90 g/ml	21.02

**Result:** The compressibility index of Atorvastatin was **21.02** %.

**Result of Hausner ratio****Table No. 6: Hausner of Atorvastatin**

S. No.	Bulk density	Tapped density	Hausner ratio
1.	0.76 g/ml	0.90 g/ml	1.26

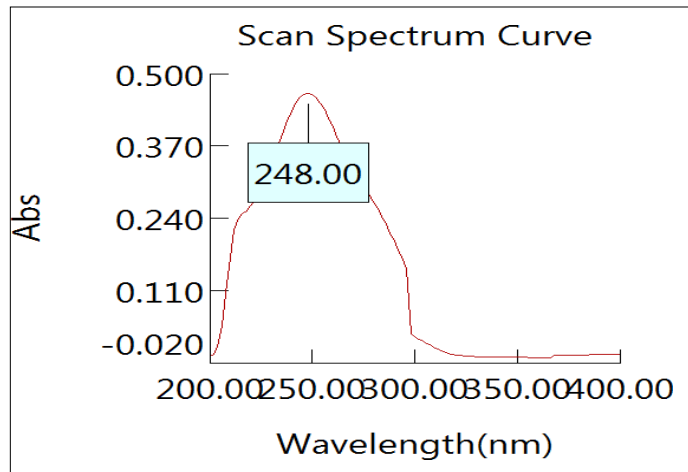
**Result:** The Hausner ratio of Atorvastatin was **1.26**.

**Moisture Content Determination:**

**Result:** The Moisture content of Atorvastatin was **0.0433**%

**Determination of  $\lambda_{\max}$  of Atorvastatin:**

The absorption maxima of Atorvastatin were determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer.

Figure 2: Determination of  $\lambda_{\max}$  of Atorvastatin at 248 nm

## Calibration curve of Atorvastatin

Table No. 7: Readings for Calibration curve of Atorvastatin

Standard Conc. ( $\mu\text{g/ml}$ )	Rep-1	Rep-2	Rep-3	Rep-4	Rep-5	Mean
5	0.098	0.099	0.097	0.098	0.098	0.098
10	0.198	0.199	0.198	0.199	0.197	0.1982
15	0.295	0.296	0.295	0.298	0.299	0.2966
20	0.389	0.389	0.391	0.398	0.399	0.3932
25	0.498	0.498	0.499	0.497	0.498	0.498
Correlation Coefficient ( $r^2$ )	0.999	0.999	0.999	0.999	0.999	0.999
Slope (m)	0.019	0.019	0.019	0.019	0.019	0.019
Intercept (c)	0	0	0	0	0	0

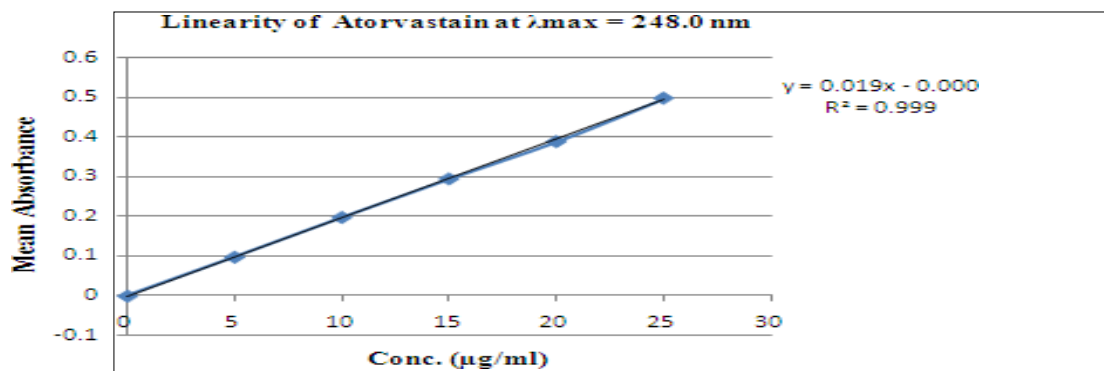


Figure 3: Calibration Curve of Atorvastatin

**Results of % solubility Enhancement****Table 8: Percentage cumulative drug release of physical mixture**

S. No.	% solubility Enhancement				
	1:1	1:2	1:3	1:4	Pure Drug
Absorbance	0.320	0.252	0.159	0.305	0.134
% Solubility Enhancement	238.806	188.0597	118.6567	227.6119	----

On the basis of % Enhancement of solubility it was concluded that solid dispersion is better option in spite of pure drug. In solid dispersion it was found that in 1:1 drug release was truly delayed which can further optimized to get better results. Therefore 1:1 ratio were found to be superior and were used for further evaluation purpose.

**Results of drug content****Table 9: Results of drug content**

Formulation	Label claim	Amount found*	Label claim (%)	S.D.	% RSD
Physical mixture	10mg	9.98	99.80	0.125	0.135

\*Average of three determination

**Results of Evaluation of prepared Film****Table 10 : Results of Evaluation of prepared Film**

Formulation code	General Appearance	Thickness in $\mu\text{m}$	Weight mg
F1	Translucent	98 $\pm$ 4	110 $\pm$ 2
F2	Translucent	102 $\pm$ 6	115 $\pm$ 5
F3	Translucent	105 $\pm$ 5	118 $\pm$ 6
F4	Translucent	95 $\pm$ 7	112 $\pm$ 7
F5	Translucent	98 $\pm$ 8	116 $\pm$ 8
F6	Translucent	105 $\pm$ 9	118 $\pm$ 9

**Result of Folding Endurance, Tensile strength & % Age Elongation****Table 11: Result of Folding Endurance, Tensile strength & % Age Elongation**

Formulation code	Folding endurance (Times)	Disintegrating time (Sec.)	Tensile strength in $\text{kg}/\text{cm}^2$	Percentage of Moisture Content	% Assay
F1	150 $\pm$ 8	100 $\pm$ 5	0.965	1.25 $\pm$ 0.32	97.85 $\pm$ 0.45
F2	165 $\pm$ 9	95 $\pm$ 8	0.895	1.65 $\pm$ 0.15	98.89 $\pm$ 0.32
F3	162 $\pm$ 7	105 $\pm$ 6	0.652	1.98 $\pm$ 0.45	95.65 $\pm$ 0.56
F4	152 $\pm$ 6	115 $\pm$ 4	0.985	0.92 $\pm$ 0.65	96.65 $\pm$ 0.45
F5	145 $\pm$ 8	68 $\pm$ 6	0.965	1.65 $\pm$ 0.58	99.56 $\pm$ 0.58
F6	189 $\pm$ 9	91 $\pm$ 5	0.978	1.45 $\pm$ 0.89	95.23 $\pm$ 0.65

**Results of optimized formulation:**

The most important criteria of present work are to that dosage form should be dissolved within few seconds. The incorporation of super disintegrating agent to minimizes the disintegrating time. Three super disintegrating agent were selected for this work.

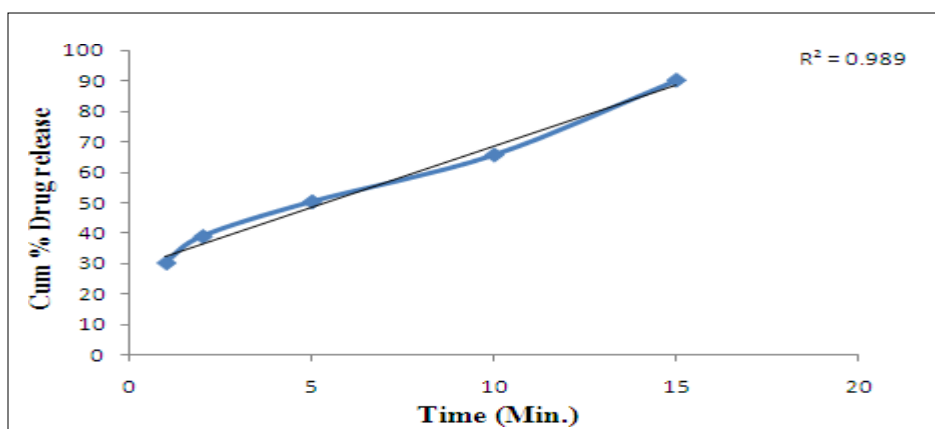
**Table 12: Results of Optimized formulation F-5**

Name of Ingredients	Composition (mg) Per Strip
API	240
HPMC K15	500
Glycerin	-
PEG-400	100
SSG	-
CCS	-
CP	150
Aspartame	50
Citric acid	100
DM water qs to	30

Results of *In-Vitro* release study of optimized formulation F5

**Table 13: Results of *In-Vitro* release study of optimized formulation F5**

S. No.	Time (Min.)	Cum % Drug release
1.	1	30.25±0.52
2.	2	38.89±0.45
3.	5	50.25±0.32
4.	10	65.56±0.65
5.	15	89.98±0.25



**Figure 4: *In-Vitro* release study of optimized formulation**

#### Results of stability studies:

Minor difference was found between evaluated parameters before and after ageing/storage and all was in acceptable limits. Therefore, formulation remains stable for sufficient time.

#### CONCLUSION:

The enhancement of dissolution rate and oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of the drug development.

Among the different methods of dissolution enhancement, Solid dispersion technology was found to be more successful with number of drugs. Solid dispersion of Atorvastatin with PEG 4000 by physical mixture method. Among the polymers used tested PEG- 4000 gave highest enhancement of dissolution rate and efficiency of Atorvastatin (1:1ratio). Further fast dissolving oral film of Atorvastatin were conveniently formulated by solvent casting method. The *in vitro* dissolution studies showed that Atorvastatin oral film formulation F5 showed maximum  $89.98 \pm 0.25$  over a period of 15 min. Overall the results of the dissolution rate studies indicated greater dissolution rate of Atorvastatin from fast dissolving oral film.

#### REFERENCES:

1. Majerik V., Horvath G., Charbit G., Badens E., Szokonya L., Bosc N., Teillaud E. (2004). Novel particle engineering techniques in drug delivery: review of formulations using supercritical fluids and liquefied gases, *Hun. J. Ind. Chem.* 32; 41–56.
2. Vemavarapu C., Mollan M.J., Lodaya M., Needhamb T.E. (2005). Design and process aspects of laboratory scale SCF particle formation systems, *Int. J. Pharm.* 292; 1–16.
3. Charbit G., Badens E., Boutin O. (2004). *Supercritical Fluid Technology for Drug Product Development, Drugs and Pharmaceutical Sciences*, 138, Marcel Dekker Inc., New York.
4. Rogers T.L., Johnston K.P., Williams R.O. III (2001). Solution-based particle formation of pharmaceutical powders by supercritical or compressed fluid CO<sub>2</sub> and cryogenic spray-freezing technologies, *Drug Dev. Ind. Pharm.* 27 (10); 1003–1015.
5. Jung J., Perrut M. (2001). Particle design using supercritical fluids: literature and patent survey, *J. Supercrit. Fluids* 20; 179–219.
6. Serajuddin, A.T.M. (1999). Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems and recent breakthroughs. *J. Pharm. Sci.* 88; 1058–1066.
7. Chiou W.L., Riegelman S. (1971). Pharmaceutical applications of solid dispersion systems. *J. Pharm. Sci.* 60; 1281–1302.
8. Ford J.L. (1986). The current status of solid dispersions. *Pharm. Acta Helv.* 61; 69–88.
9. Serajuddin, A.T.M., Sheen P.C., Mufson D., Bernstein D.F., Augustine M.A. (1988a). Effect of vehicle amphiphilicity on the dissolution and bioavailability of a poorly water-soluble drug from solid dispersions. *J. Pharm. Sci.* 77; 414–417.
10. Kakumanu V. K., Bansal A. K. (2004). *Supercritical Fluid Technology in Pharmaceutical Research*. *Businessbriefing: Labtech*, 70–72.