

# **INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES**

**Pharmaceutical Sciences**

**Research Article.....!!!**

Received: 29-07-2021; Revised: 30-09-2021; Accepted: 13-10-2021

## **SOLUBILITY ENHANCEMENT OF ATORVASTATIN CALCIUM BY USING NATURAL CARRIER**

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### **Keywords:**

Atorvastatin Calcium,  
Lyophilisation,  
Solubility, Solid  
Dispersion

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### **ABSTRACT**

Atorvastatin calcium is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. According to the biopharmaceutical classification, ATR comes under Class II (low solubility and high permeability). Because of the limited aqueous solubility, it exhibits dissolution rate limited oral absorption. The objective of this investigation was to improve the solubility of the poorly water soluble drug atorvastatin (ATR), using solid dispersion (SD) techniques, with *Aegel marmelos* Gum (AMG) as a hydrophilic carrier. The effect of two variables related to solid dispersions preparation (drug to carrier ratio and method of preparation) were investigated. All the SDs prepared by Cogrounding, Solvent evaporation and Lyophilisation techniques showed remarkable increase in the solubility compared to the pure ATR. The solubility analysis demonstrated highest increase in the solubility of drug observed with ATR-AMG ratio 1:1 by lyophilisation technique. During In Vitro study result obtained that the SD prepared using the Lyophilization method containing 1:1 ATR-AMG ratio displays faster dissolution rates compared with those prepared using the other that is 98.8±0.09% drug release within 90 min. The SD was characterized using DSC and XRD technique.

## 1. INTRODUCTION

In recent years, the formulation of poorly soluble compounds presented interesting challenges for formulation scientists in the pharmaceutical industry. Up to 40% of new chemical entities discovered by the pharmaceutical industry are poorly soluble or lipophilic compounds, which lead to poor oral bioavailability.

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Atorvastatin calcium is a synthetic lipid-lowering agent. [1-3] Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. According to the biopharmaceutical classification, ATR comes under Class II (low solubility and high permeability). Because of the limited aqueous solubility, it exhibits dissolution rate limited oral absorption. [10,11,12]

Solid dispersion techniques have been used to enhance the dissolution and oral bioavailability of many poorly water soluble drugs. [4,5] To overcome the solubility problem, many authors formulated solid dispersions using number of various polymers and methods. In spite of tremendous

research activity on solid dispersions since 1961, their commercial application is limited. Only a few products have been marketed so far. [6,7,8,9]

One aspect of solid dispersion technology on which most workers in the field would agree is that the number of marketed products arising from this approach has been disappointing. Research for alternative carriers has been increasing to suit for the industrial applications as well as to reduce the production cost and toxic effects. Recently, many natural polymers have been evaluated for their uses in formulation of solid dispersion. Cost effective pharmaceutical excipients are always desirable. [13,14]

Pharmaceutical excipients developed from natural sources are economic. Present day consumers look for natural ingredients in food, drugs and cosmetics as they believe that anything natural will be more safe and devoid of side effects. [15,16] Natural excipients show lack of toxicity, easy availability and economic considerations in pharmaceutical industry as compared to their synthetic counterparts. Naturally, derived excipients have shown promising results in the modification of drug release from the formulations. [17,18]

*Aegel marmelos* Gum (AMG) is a natural polymer that is obtained from fruits of

*Aegle marmelos* belonging to family Rutaceae is indigenous to India.. AMG has been investigated for use as a tablet binder and mucoadhesive agent. AMG is widely used because of its high swelling index, high water retention capacity, digestible nature, binding ability, and easy availability. [19-20]

The objective of this investigation was to improve the solubility of the poorly water soluble drug atorvastatin (ATR), using solid dispersion (SD) techniques, with *Aegle marmelos* Gum (AMG) as a hydrophilic carrier. The effect of two variables related to solid dispersions preparation (drug to carrier ratio and method of preparation) were investigated. The apparent solubility was investigated, and in vitro dissolution studies were performed. DSC and XRD studies were also carried out.

**2. MATERIALS AND METHODS**  
Atorvastatin calcium gift sample was provided by Zydus Cadila Healthcare, Ahmedabad, India. *Aegle marmelos* fruits were collected from nearby locality of Pune region of Maharashtra, India. Other chemicals used were of analytical grade.

**2.1. Isolation and Purification of *Aegle marmelos* gum:**

**2.2.** Fresh pulpy parts of edible fruits of *Aegle marmelos* were soaked in distilled water and boiled for 2-3 hours in a water bath until slurry was

formed. The slurry was cooled and kept in refrigerator overnight so that most of the undissolved portion was settled out. The upper clear supernatant solution was decanted off and concentrated at 60°C on a water bath until the volume reduced to its one third. Solution was cooled down to the room temperature and was poured into thrice the volume of acetone by continuous stirring. The precipitate was washed repeatedly with acetone and dried at 50°C. The dried gum was powdered and stored in tightly closed container for further use. [19,20]

**2.3. Characterization of *Aegle marmelos* Gum** [20,25]

**a. Macroscopic property.** Color, Taste, Odor

**b. Solubility.** Small amount of AMG powder added into 5ml solvent and solubility checked visually.

**c. Swelling Index.** AMG (1 g) was weighed accurately and transferred to a 100mL measuring cylinder. The initial volume of the powder was noted. Then the gum was dispersed thoroughly in distilled water by vigorous shaking. The measuring cylinder was maintained for 24 hours at ambient temperature and humidity. The volume occupied by the AMG sediment after 24 hours was noted. The swelling index, expressed as a percentage, was calculated according to the following equation:

$$SI = (X1 - X0/X0) \times 100$$

Where X0 is the initial height of the powder in the graduated cylinder and X1 is the height of the swollen gum after 24 hours.

**d. Water Retention Capacity.** After the swelling index study was carried out, the content of the measuring cylinder was filtered using a muslin cloth, and the water was allowed to drain completely into a dry 100mL graduated cylinder. The volume of the water collected was noted. The water retained by the sample was determined as the difference between the original volume of the mucilage and the volume of the drained water. The amount of water retained per unit volume of a polysaccharide is referred to as its water retention capacity or water absorption capacity.

**e. Viscosity Measurement.** The viscosity of a 1% aqueous AMG solution was measured according to USP specifications using a Brookfield DV-E viscometer.

**f. Angle of Repose.** The angle of repose was measured using the fixed funnel method. An accurately weighed quantity of powdered gum was poured through a funnel. The height of the funnel was adjusted such that its tip just touched the top of the heap of powder below it. The powder was

allowed to flow through the funnel freely on to the heap of powder, and the angle of repose was calculated using the following equation:

$$\tan\theta = h/r$$

Where  $h$  is the height of the heap of powder and  $r$  is the radius of the heap of powder.

**g. Density.** The loose bulk density (LBD) and tapped bulk density (TBD) of the AMG powder were determined. Powdered gum (5 g) was poured into a calibrated measuring cylinder (10mL capacity), and the initial volume was noted. Then the cylinder was dropped onto a hard surface from a height of 2.5 cm at 2-second intervals. The tapping was continued until no further change in volume was noted. The LBD and TBD were calculated using the following equation

LBD = Weight of the powder / Initial volume of the packing

TBD = Weight of the powder / Tapped volume of the packing

**h. Compressibility index.** The compressibility index (Carr's index) was determined using the following equation:

$$\text{Carr's index (\%)} = [(TBD - LBD / TBD)] \times 100.$$

#### 2.4. Methods of Preparation of SD

A physical mixture (PM) of AMG and ATR was prepared by simple blending using a spatula. The PM was passed through a 100# sieve.

**2.4.1. Co-grinding method.**

Solid dispersion were prepared by thoroughly grinding accurately weighed quantities of ATC and AMG in various ratios (1:1 and 1:2) for 20-30 minutes in glass mortar individually. The dispersions were then sifted through sieve no.80 and stored in desiccators till further use. [21]

**2.4.2. Solvent evaporation method.**

ATR was dissolved in ethanol until saturation, and stirring was continued for 30 minutes. AMG was suspended in a sufficient quantity of water until a wet mass of polymer was formed. The solution of the drug was poured at into polymer suspension immediately after it was formed. All the solvent was removed by evaporation at 60°C. [22,24]

**2.4.3. Lyophilisation technique.** The earlier prepared 1:1 and 1:2 physical mixtures of the ATR and AMG were wetted with 1:1 water: methanol mixture and this was kneaded to form a homogeneous suspension. This was then frozen and subjected to lyophilisation for 24hrs at -540C. The final product was then pulverized and sifted through sieve no. 80. [23]

**2.5. Characterization of SDs****2.5.1. Estimation of Drug Content.**

Quantities of the physical mixtures (Equivalent to 20 mg of ATR) produced using the cogrinding, solvent evaporation and lyophillisation

methods were dissolved in 100mL of phosphate buffer solution of pH 6.8. The samples were filtered through a 0.45  $\mu\text{m}$  membrane filter. It was then diluted appropriately with the solvent and the drug content of each was determined spectrophotometrically at 241 nm. Phosphate buffer solution (pH 6.8) was used as the blank.

**2.5.2. Solubility Study.**

Solubility study was performed according to method reported by Higuchi and Connors. The solubility data of SD prepared using the cogrinding, solvent evaporation and lyophillisation methods in phosphate buffer solution (pH 6.8) were determined. Quantities of the SD equivalent to 20mg of the drug were added to 10 ml Phosphate Buffer Ph 6.8 taken in glass vials with cap and shaken for 24 hrs. The vials were kept on a orbital shaker maintained at  $37\pm 0.5^\circ\text{C}$  for 24 h. After shaking, the vials were kept equilibrated at  $37\pm 0.5^\circ\text{C}$  for 12 h. Then, the solution was filtered through a 0.45- $\mu\text{m}$  millipore filter and the filtrate was assayed spectrophotometrically at 241nm. It was then diluted appropriately with the solvent and its absorption was observed through UV spectrophotometer at 241nm.

**2.5.3. In Vitro Drug Release Study.**

The dissolution rates of the different SD were determined using

900mL of phosphate buffer solution (pH 6.8) at  $37 \pm 0.5^\circ\text{C}$  using a type II USP dissolution test apparatus (EDT-08L-Electrolab, Mumbai, India) run at 75 rpm. 5ml aliquots of the dissolution medium were withdrawn at 10, 20, 30, 40, 50, 60, 70, 80 and 90 minutes. The samples were suitably diluted and analyzed spectrophotometrically at 241 nm.

**2.5.4. Infrared Spectroscopy.** The Infrared spectroscopy of the pure ATR, AMG and optimized SD was carried out to ascertain identity of the drugs. The drug powder was placed on IR compartment and scanned between wave number  $4000-1 - 500 \text{ cm}^{-1}$  using a Shimadzu Model 8400 FTIR with ATR.

**2.5.5. X-Ray Diffraction Studies.** Powder XRD patterns of pure ATR, AMG and optimized SD were recorded using a diffractometer. The diffractometer ( Bruker D5) was run at a scanning speed of  $2^\circ/\text{mm}$  and a chart speed of  $2^\circ/2 \text{ cm per } 2\theta$ .

**2.5.6. DSC Thermo gram.** DSC thermogram of pure ATR, AMG and optimized SD were obtained using a differential scanning calorimeter with a heating rate of  $100^\circ\text{C}/\text{minute}$  from  $50^\circ\text{C}$  to  $200^\circ\text{C}$  in a nitrogen atmosphere using Mettler Toledo DSC-1 Thermal Analyzer in nitrogen atmosphere.

### 3. RESULT AND DISCUSSION

**3.1. Polymer Characterization.** The results of the AMG characterization studies are listed in Table 1. AMG has a low viscosity and high water retention capacity. The water retention capacity of a carrier is the amount of water retained in it which indicates the hydrophilic nature of the carrier. Low viscosity of AMG makes it suitable candidate for solubility and bioavailability enhancement of poorly water soluble drugs.

**Table 1: AMG Characterization**

Parameters		<i>Aegel marmelos</i> Gum
Macroscopic property	Color	Light Brown color
	Taste	Sweet
	Odour	Characteristic sweetish
Solubility	Water	Soluble
	Acetone	Insoluble
	Ethanol	Insoluble
	Chloroform	Insoluble
Swelling index (%)		$27.5 \pm 2.5$
Water retention capacity (mL)		$7.71 \pm 0.175$
Viscosity (cps)		$303 \pm 2.645$
Angle of repose		$32.46 \pm 1.17$
Density		
(1) Bulk density		$0.58 \pm 0.02$
(2) Tapped density		$0.66 \pm 0.02$
Carr's index (%)		$12.73 \pm 5.35$

$n = 3$



1. **Estimation of Drug content.** The drug content of the SD and the PM is provided in Table 2. The results clearly suggest that the drug content of each formulation is within the theoretical range, indicating that the method used to prepare the formulations is suitable and reproducible in nature.

**Table 2: Estimation of drug content**

RATIO (ATR+AMG)	PM	CO	SE	LYO
1:1	98.40±0.8	99.69±1.060	99.63±0.31	99.11±1.165
1:2	99.45±1.36	99.02±2.078	97.87±0.26	99.97±0.657

$n = 3$ ; ATR: atorvastatin; PM: physical mixture; CO: Cogrinding, SE: solvent evaporation; and

LYO: Lyophilisation method

2. **Solubility Study.** The solubility values of different SDs containing ATR+AMG (1:1) and ATR+AMG (1:2) are reported in Table 3 and Table 4. The solubility of ATR has definitely increased in presence of AMG. The method of preparation and ratio with AMG also had definite impact on the solubility of ATR. It followed following pattern for solubility enhancement of ATR.

**Method:** Lyophilization method > Cogrinding > Solvent evaporation > Physical Mixture

**Ratio of ATR-AMG = 1:1 > 1:2**

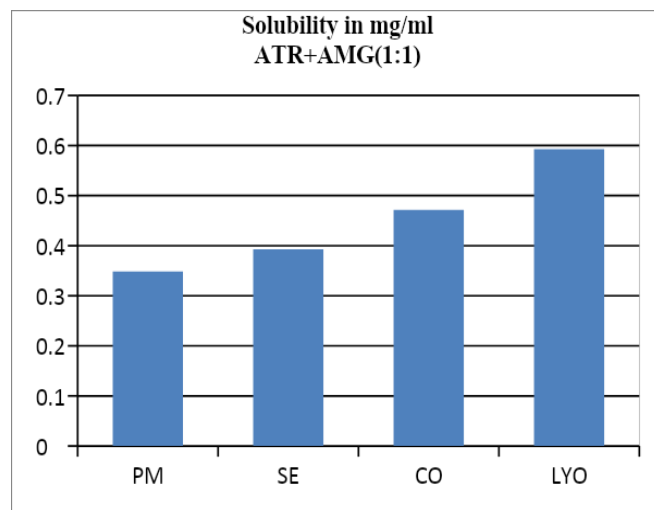
The SD prepared using the Lyophilisation method containing ATR-AMG in proportion of 1:1 ratio displays

highest solubility compared with those prepared using the other. (Figure 1 and Figure 2)

**Table 3: Solubility Values for Various SDs with ATR + AMG (1:1) in Phosphate Buffer (pH=6.8)**

Sr .No	Method	Solubility (mg/ml)
1	Physical Mixture (PM)	0.348791±0.012432
2	Solvent evaporation technique(SE)	0.3928 ±0.0156
3	Cogrinding method(CO)	0.4718±0.0002
4	Lyophilization method(LYO)	0.59301±0.015004

\*All values are expressed as mean ±SD,  $n=3$

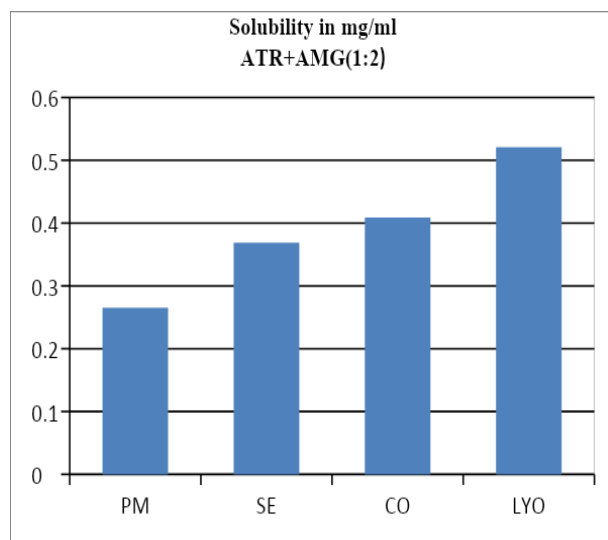


**Figure 1: Bar Diagram for Solubility Values for Various SDs with ATR + AMG (1:1) in Phosphate Buffer (pH=6.8)**

**Table 4: Solubility Values for Various SDs with ATR + AMG (1:2) in Phosphate Buffer (pH=6.8)**

Sr .No	Method	Solubility (mg/ml)
1	Physical Mixture	0.265±0.004242
2	Solvent evaporation technique	0.3685±0.00919
3	Cogrinding method	0.40905±0.00968
4	Lyophilization method	0.521±0.0395

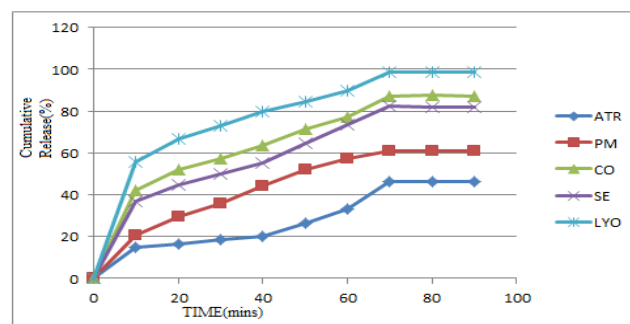
\*All values are expressed as mean ±SD, n=3



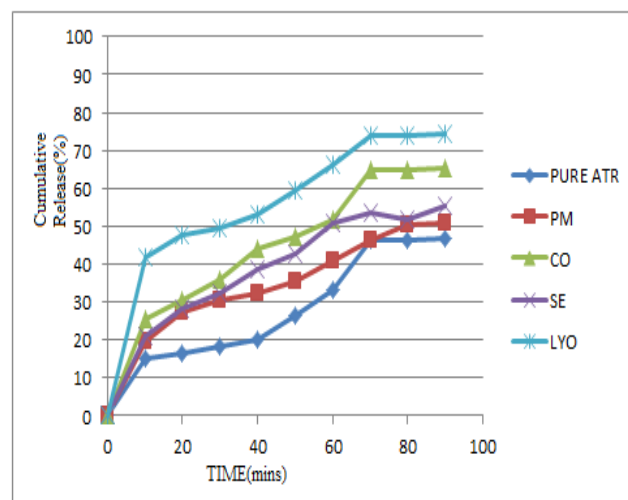
**Figure 2: Bar Diagram for Solubility Values for Various SDs with ATR + AMG (1:2) in Phosphate Buffer (pH=6.8)**

3. **In Vitro Drug Release Study.** The in vitro drug release profiles of ATR, the PM, and the SD prepared using the Cogrinding, Solvent evaporation and Lyophilisation

methods with AMG as the hydrophilic carrier are shown in Figure 3 and 4. The SD prepared using the Lyophilization method containing 1:1 ATR: AMG ratio displays faster dissolution rates compared with those prepared using the other. On the basis of results of solubility and dissolution study SD prepared by Lyophilization method containing ATR: AMG in proportion of 1:1 ratio was used for further characterization.



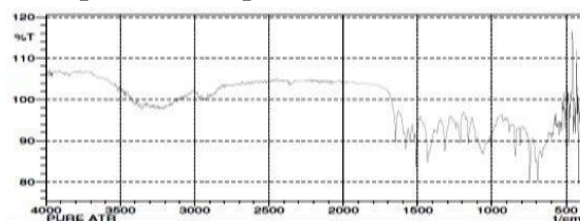
**Figure 3: Dissolution Data for Various SDs with ATR + AMG (1:1) in Phosphate Buffer (pH=6.8)**



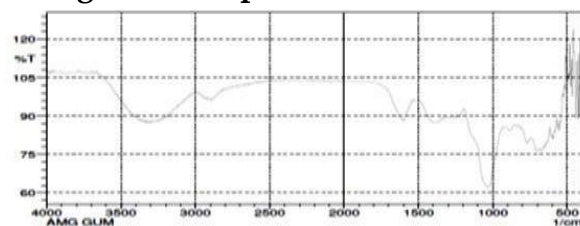
**Figure 4: Dissolution Data for Various SDs with ATR + AMG (1:2) in Phosphate Buffer (pH=6.8)**



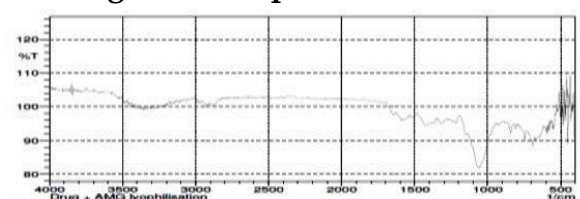
**4. Infrared Spectroscopy.** IR spectrum was taken by ATR technique and graph is shown in **Figure 5, 6 and 7**. The IR spectra of mixture of ATR + AMG (1:1) SD prepared using lyophilisation shows peaks at 1317  $\text{cm}^{-1}$  for C-N (stre), 1647  $\text{cm}^{-1}$  for C=O, 1581  $\text{cm}^{-1}$  for N-H (bend), 1055.06  $\text{cm}^{-1}$  for C-O (Stre), 3410.5  $\text{cm}^{-1}$  O-H (stre), 2933.7  $\text{cm}^{-1}$  for  $-\text{CH}_3$  and other important peaks are seen. The spectra indicated intact peaks for pure ATR as well as pure AMG. In all cases however, there was reduction in intensity of ATR peak which is indicating formation of SDs. This shows that there is no difference in the absorption band position.



**Figure 5: IR spectra of Pure ATR**

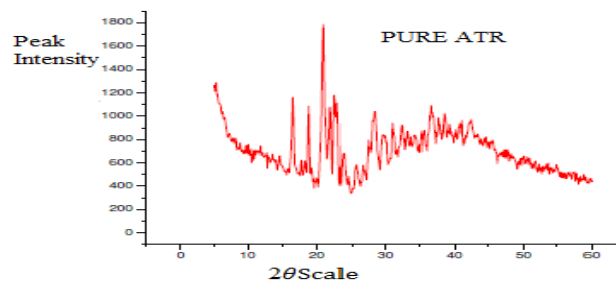


**Figure 6: IR spectra of AMG**

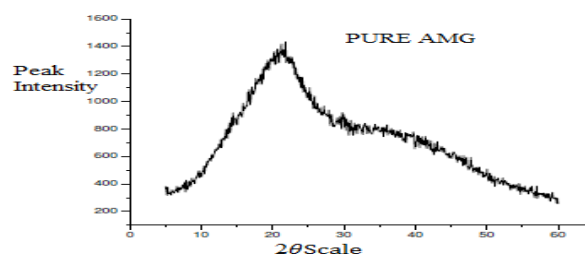


**Figure 7: IR Spectra ATR+AMG (1:1) Solid dispersion using Lyophilization method**

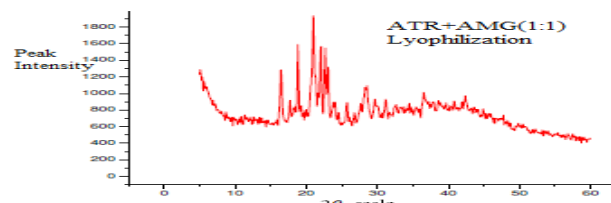
**5. X Ray Diffraction Studies.** The X-ray diffractogram of ATR shows sharp and intense peaks at diffraction angles ( $2\theta$ ) of 16.23°, 20.91°, 22.6°, 28.56°, 36.32° suggesting a typical crystalline pattern. The X-ray diffractogram of AMG shows broad peaks suggesting its amorphous nature. Few characteristic crystalline peaks appear in the diffractograms of the SD but at low intensity. This proves that the crystallinity of ATR decreases as most of the drug gets converted to an amorphous form. (**Figure: 8, 9 and 10**).



**Figure 8: XRD of Pure ATR**

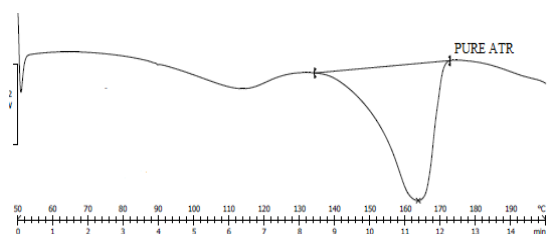


**Figure 9: XRD of Aegel marmelos gum**

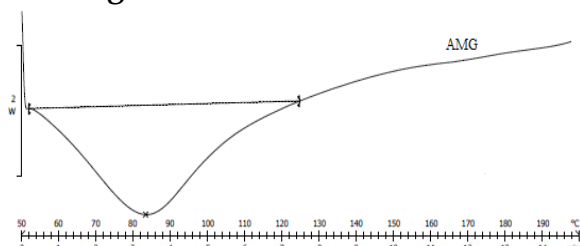


**Figure 10: XRD of ATR+AMG (1:1) Solid dispersion using Lyophilization method**

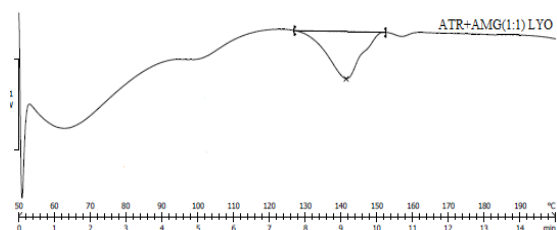
**6. DSC Thermo gram.** The DSC thermograms of ATR, AMG and SD (produced using the lyophilisation method) are shown in **Figure 11, 12 and 13**. The thermograms of ATR exhibit an endothermic peak at 163.6°C, corresponding to its melting point, while AMG exhibits a broad endothermic peak owing to its amorphous nature. The broad endothermic peak of ATR was observed at 141°C in the thermo gram of SD, suggesting that the crystalline form was converted to the amorphous one.



**Figure 11: DSC of Pure ATR**



**Figure 12: DSC of Aegel marmelos gum**



**Figure 13: DSC of ATR+AMG (1:1) Solid dispersion using Lyophilization method**

## CONCLUSION

Solid dispersions significantly improved the dissolution profiles. All the SDs prepared by Cogrinding, Solvent evaporation and Lyophilisation techniques showed remarkable increase in the solubility compared to the pure ATR. IR and UV spectral analysis results indicated that there was no probable interaction between drug and carrier. XRD, DSC studies showed almost inhibition of crystallinity in ATR solid dispersions with AMG. The SD prepared using the Lyophilisation method containing 1:1 ATR: AMG ratio displays faster dissolution rates compared with those prepared using the other. In conclusion, AMG could be used as a potential natural carrier to enhance the rate of dissolution of ATR.

## ACKNOWLEDGEMENTS

The authors are grateful to the Principal and Management of Marathwada Mitra Mandal's College of Pharmacy, Thergaon (Kalewadi), Pune, for providing all necessary facilities and infrastructure to carry out this study. The authors also acknowledge Zydus Cadila Healthcare, Ahmedabad, India for providing gift sample of, Atorvastatin Calcium.

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#### HOW TO CITE THIS ARTICLE

Jagtap PV, Sonwalkar SG, Yadav MB, Bangar BN, Kodalkar DD: Solubility Enhancement of Atorvastatin Calcium by Using Natural Carrier. International Journal of Institutional Pharmacy and Life Sciences, Vol 11[5] September-October 2021 : 15-25.