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# Solubility Enhancement of Atorvastatin Tablets by Solid Dispersions Using Fenugreek Seed Mucilage

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## Abstract

Fenugreek seed mucilage (FSM) is isolated from the seeds of *Trigonella Foenum-graecum*, commonly known as Fenugreek, which is herbaceous plant. Fenugreek seeds contain high percentage of mucilage, which does not dissolve in water, but swell up and become slick when exposed to fluids. Atorvastatin is one of the HMG-CoA reductase inhibitors (statins), which are lipid-lowering medications used in the primary and secondary prevention of coronary heart disease. Atorvastatin is poorly absorbed orally, its oral bioavailability is very low (about14%) because it is very slightly soluble in distilled water and pH 7.4 phosphate buffer, which would limit its clinical application. The objective of this study is to enhance atorvastatin solubility in order to increase its bioavailability by the formulation of solid dispersion using fenugreek seed mucilage. Mucilage was extracted from the seed and evaluated for flow properties, pH value, FTIR spectroscopy and percentage practical yield. Then solid dispersions with different drug to polymer ratios were prepared from fenugreek mucilage and hydroxy propyl methyl cellulose (HPMC), after that saturation solubility was tested for fenugreek seed mucilage solid dispersion (FSMSD), hydroxxy propyle methyl cellulose solid dispersion (HPMCSD) and pure drug. Tablets were prepared from solid dispersion with the highest saturation solubility, then tablets were tested and evaluated. The tablets showed satisfactory physicochemical properties as 1.77%RSD in tablet weight variation, 1 min disintegration time, 5.24±0.457 Hardness and 89% drug release in 45 min. it is concluded that FSM is a promising excipient that can be used in dosage forms formulation to enhance solubility of low soluble drugs.

**Keywords:** Solubility, mucilage, fenugreek, bioavailability, solid dispersion.

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## INTRODUCTION

### Atorvastatin

Is one of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) which are lipid-lowering medications used in the primary and secondary prevention of coronary heart disease. Atorvastatin competitively inhibits (HMG-CoA) reductase. By preventing the conversion of HMG-CoA to mevalonate, statin medications decrease cholesterol production in the liver [1]

Atorvastatin is rapidly absorbed after oral administration with a peak plasma concentration at 1 to 2 hours. The bioavailability is low (about 14%). Atorvastatin is classified according to Bio-pharmaceutical Classification System (BCS) as class II.

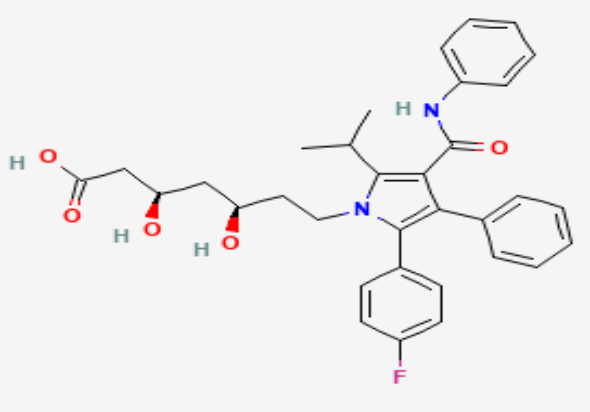


**Fig 1: Atorvastatin chemical structure**

### Fenugreek seed mucilage (FSM)

Mucilage is obtained from the seeds of *Trigonella Foenum-graecum*, commonly known as

Fenugreek, Which is herbaceous plant (family: *Leguminosae*). Fenugreek seeds contain a high percentage of mucilage (a natural gummy substance present in the coatings of many seeds). Although it does not dissolve in water, mucilage forms a viscous tacky mass when exposed to fluids. Like other mucilage-containing substances, fenugreek seeds swell up and become slick when they are exposed to fluids [2, 3].

**Bio availability**

The term Bioavailability is a principal pharmacokinetic property of drugs. It used to describe the fraction of unchanged drug that reaches the systemic circulation. By definition, when a medication is administered intravenously, its bioavailability is 100%. However, when a medication is administered through other routes (such as oral), its bioavailability decreases (due to incomplete absorption or first-pass metabolism). The measurement of the amount of the drug in the plasma at periodic time intervals indirectly indicates the rate and extent at which the active pharmaceutical ingredient is absorbed from the dosage form and becomes available at the site of action. Bioavailability is an essential tool in pharmacokinetics, as it must be considered when calculating dosages for non-intravenous routes of administration. It is expressed as either absolute or relative bioavailability [4].

**Bio-pharmaceutical Classification System (BCS)**

Is a scientific framework to classify drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from Immediate Release solid oral dosage forms: (1) dissolution, (2) solubility, and (3) intestinal permeability [5]. According to the BCS, drug substances were classified as follows [6]:

- Class 1: High Solubility – High Permeability.
- Class II: Low Solubility – High Permeability.
- Class III: High Solubility – Low Permeability.
- Class IV: Low Solubility – Low Permeability.

In addition, some immediate release (IR) solid oral dosage forms are categorized as having rapid or very rapid dissolution [7].

**Solubility Enhancement of BCS Class II Drugs:**

The solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature. Various techniques are available to improve the solubility of poorly soluble drugs [8]. These techniques can be categorized in three basic approaches:

1. Traditional Techniques.
2. Newer and Novel Techniques.
3. Solid Dispersion Technique.

**Solid Dispersion System**

Solid dispersion is one of the techniques of solubility enhancement in which poorly water-soluble drugs is dispersed in an inert hydrophilic carrier at solid state provided by the different method like melting, solvent, or solvent-melting method. This technique advocated the application of glass solution to increase dissolution rates. The solid dispersion provides the possibility of reducing the particle size of such drugs to nearly a molecular level, to transform the drug from the crystalline to the (partial) amorphous state, and/or to locally increase the saturation solubility. It means that solid dispersion enhances the bioavailability of water insoluble drugs by increasing their saturation solubility in the gastrointestinal fluids [9**].**

**Materials:**

- Atorvastatin working standard powder (ATVS) and Atorvastatin calcium powder (ATV) were kindly gifted from Azal pharmaceutical industries Co.Ltd, Khartoum north.
- Hydroxy-propyl methyl cellulose (HPMC) was obtained as gift sample from Blue Nile pharmaceutical factory, Khartoum north.
- Fenugreek seeds was purchased from local market.

All reagents used were of analytical grade.

**Method:**

**Preparation of Atorvastatin solid dispersions with HPMC:** Accurately weighed quantities of Atorvastatin and HPMC (1:2, 1:4 and 1:6 drug to polymer ratio) were mixed and dissolved in water to get a solution then the solvent was evaporated using freeze dryer until dry, then crushed and sieved (75-150µm) and finally stored in desiccators silica gel till further use.

**Extraction of Fenugreek seed mucilage (FSM):** Fenugreek seed mucilage (FSM) was isolated by soaking 100 g of fenugreek seeds in distilled water (0.75 L) for 12 h at room temperature and then boiled until the formation of slurry. The slurry was kept in the refrigerator for another 12 h, the upper clear solution was decanted and concentrated on water bath to 1/3 of its original volume. The solution was cooled at room temperature then poured into absolute ethanol, under continuous stirring. The precipitate was washed several times with ethanol, then dried using freeze dryer and kept over silica gel, in desiccators until further use.

**Preparation of Atorvastatin solid dispersion with FSM:** Accurately weighed quantities of Atorvastatin and FSM (1:2, 1:4 and 1:6 drug to polymer ratio) were mixed and dissolved in suitable amounts of water then the solvent was evaporated using freeze dryer until dry, then crushed and sieved(75-150µm) and finally stored in a desiccators silica gel till further use**.**

**Evaluation of solid dispersion:**

**Percentage yield determination:** Mucilage was extracted and isolated from 100 g of raw material. The isolated mucilage was then dried well and percentage yield was calculated by following formula:

$$\%\, Yield = \frac{Practical\ Yield}{Theoretical\ Yield} \text{ X } 100$$

**Determination of flow properties; Bulk density and tapped density:** Accurately weighed amount of solid dispersions were transferred to 100 ml graduated cylinder to measure the apparent volume (bulk volume: Vb). The cylinder was then tapped for a fixed period of time and tapped volume (Vt) occupied in the cylinder was measured. The bulk density and tapped density were calculated in gm /ml using the following formula:

Bulk density= $\frac{Mass}{Volume} = \frac{M}{V}$

Tabbed Density TD= $\frac{Mass}{Tapped\ volume} = \frac{M}{Vt}$

**Carr's Index (CI) and Hausner's ratio (HR):** Carr's index and Hausner's ratio are calculated by using the following formulae [10, 11]:

CI =[ $\frac{Tapped\ density - bulk\ density}{tapped\ density}$] X 100

Hausner's ratio=$\frac{Tapped\ Density}{Bulk\ density}$

**Angle of repose:** A funnel was fixed in the stand in such a way that the top of the funnel was at the height of 6 cm from the surface. The solid dispersions were passed through the funnel. The height and radius of the heap were measured and the angle of repose was calculated using the following equation [12].

$\Theta = \tan^{-1} (\frac{h}{r})$

- h = Height of heap
- r = Radius of the heap

**Fourier Transform Infrared (FTIR) Spectroscopy test:** Atorvastatin and the other two prepared solid dispersions were characterized using FTIR spectroscopy. KBr discs were prepared by mixing the sample with potassium bromide powder in the ratio 1:9 sample to KBr, then compressed into thin disk by using hydrostatic press model HP15, which then tested in IR Affinity 1(Shimadzu, Japan) instrument. Data was recorded over the spectral range 500- 4000 Cm $^{-1}$ and resolution 4 Cm̄ $^{1}$.

**Determination of wavelength (λ max):** 1 mg/ ml solution of atorvastatin calcium in 50% acetonitrile solution in water was prepared as a stock solution. from the stock solution1 ml was withdrawn and completed to 100 ml with water to obtain 10 µg /ml final solution. UV spectrum was recorded in the wavelength range of 200 - 400nm. Wavelength of maximum absorbance was determined (Fig 1).

**Construction of calibration curve:** From the stock solution prepared previously, 1,1.2, 1.4, 1.6 and 1.8 ml aliquots were withdrawn respectively and the volume made up to 100 ml with water to obtain the solutions with concentrations 10, 12,14, 16, 18 µg /ml respectively. UV absorbance was recorded for each solution at λ max 240 nm.

**Drug content determination:** Solid dispersions equivalent to 20 mg atorvastatin were weighed accurately, dissolved in 100 ml of phosphate buffer, filtered, diluted, then drug content was analyzed at λ max 240 nm against blank using UV spectrophotometer. Actual drug contents were calculated using the equation:

Percent Drug content: $\frac{actual\ amount\ of\ drug}{t\ heoratical\ amount\ of\ drug}$X100%

**Preparation of atorvastatin tablet from solid dispersion:**

Atorvastatin tablets were prepared by wet granulation method, as specified in the table of formulation (Table-1). Accurately weighed quantities of solid dispersion, lactose, sodium starch glycolate (primogel) and MCC were mixed, sifted and wetted with sufficient amount of water to form wet mass, then forced manually through a mesh screen No 8 to form large granules, which then dried at 60°C for 30 min in the oven, crushed and passed through mesh No 12. Mg stearate and talc powder were mixed with dry granules and finally compressed on an 8 mm punch and die using single punch tableting machine (Shakti, India).

**Tablet evaluation:**

**Weight variation test:** Twenty tablets were weighed individually using sensitive balance; the weights were reported. the mean was calculated and standard deviation was calculated using the equation [13]:

$$S = \sqrt{\frac{\Sigma \left(X - \overline{X}\right)^2}{n-1}}$$

And percentage relative standard deviation using the equation: (%RSD) = $\frac{S}{X} \times 100$

The results were recorded in (Table-5).

**Hardness test:** The resistance of the tablet to breakage was determined (mean ± %RSD) using the Hardness Tester (YD-20KZ).10 tablets were tested, the results were recorded in term of Kg/cm².

- Limits: 4 Kg/cm² minimum and 6 Kg/cm² maximum

**Friability test:** Friability of the tablets was estimated using friabilator apparatus (FT-2000SE). 20 tablets were weighed accurately then placed in the plastic cavity of the apparatus which rotated for 4 min in the speed 25 rpm. The dust was removed using a soft

muslin cloth and then reweighed. The friability was calculated using the formula:

Friability% = $\frac{(w1-w2)}{w1}$ X100

Where:
$w1$: initial weight of tablets.
$w2$: weight after friability.

The results were recorded (Table-5).

**Limits:** Generally, the test is run once. If obviously cracked, cleaved or broken tablets are present in the sample after tumbling, the sample fails the test. If the results are difficult to interpret or if the weight loss is greater than the targeted value, the test should be repeated twice and the mean of the three tests determined. Maximum mean weight loss of the three samples of not more than 1% is considered acceptable for most products [14].

**Disintegration test:** Six randomly selected tablets of each brand were placed on the mesh of the six beakers of the disintegration tester (TDTF ZBS-6E) in water as immersion media at 37º C, and the time adjusted at 30 min. The time required for absence of tablet residue from the surface of the mesh was recorded as the disintegration time [15]. The results were recorded in (Table-5).

**Invitro dissolution study:** The dissolution rates of the tablet prepared were studied in 900 ml phosphate buffer pH 6.8 using USP type II dissolution test apparatus with a paddle stirrer at 75 rpm. A temperature 37±0.5°C was maintained throughout the study. each sample was tested in 6 flasks and the mean absorbance was recorded. Samples of dissolution media (10ml) were withdrawn through syringe filters (0.45µ) at different time- intervals (5, 10, 30, 45, 60 min) and directly assayed at ƛ 240 nm. The samples of dissolution fluid withdrawn at each time were replaced with fresh buffer fluid [16]. The concentration of each sample and the amount of drug in the sample were calculated (Table-3). Finally, the percent of drug released was calculated and plotted against time in a dissolution profile (Fig 8).

## RESULTS AND CALCULATIONS

**Determination of the polymers flow properties:**

**Table-1: flow properties of the polymers**

| Property | Bulk density | Tapped density | Carr's Index | Hausner's ratio | Angle of repose | PH value |
|---|---|---|---|---|---|---|
| **Value** | 0.181 | 0.25 | 25 | 1.38 | 17 | 6.1 |

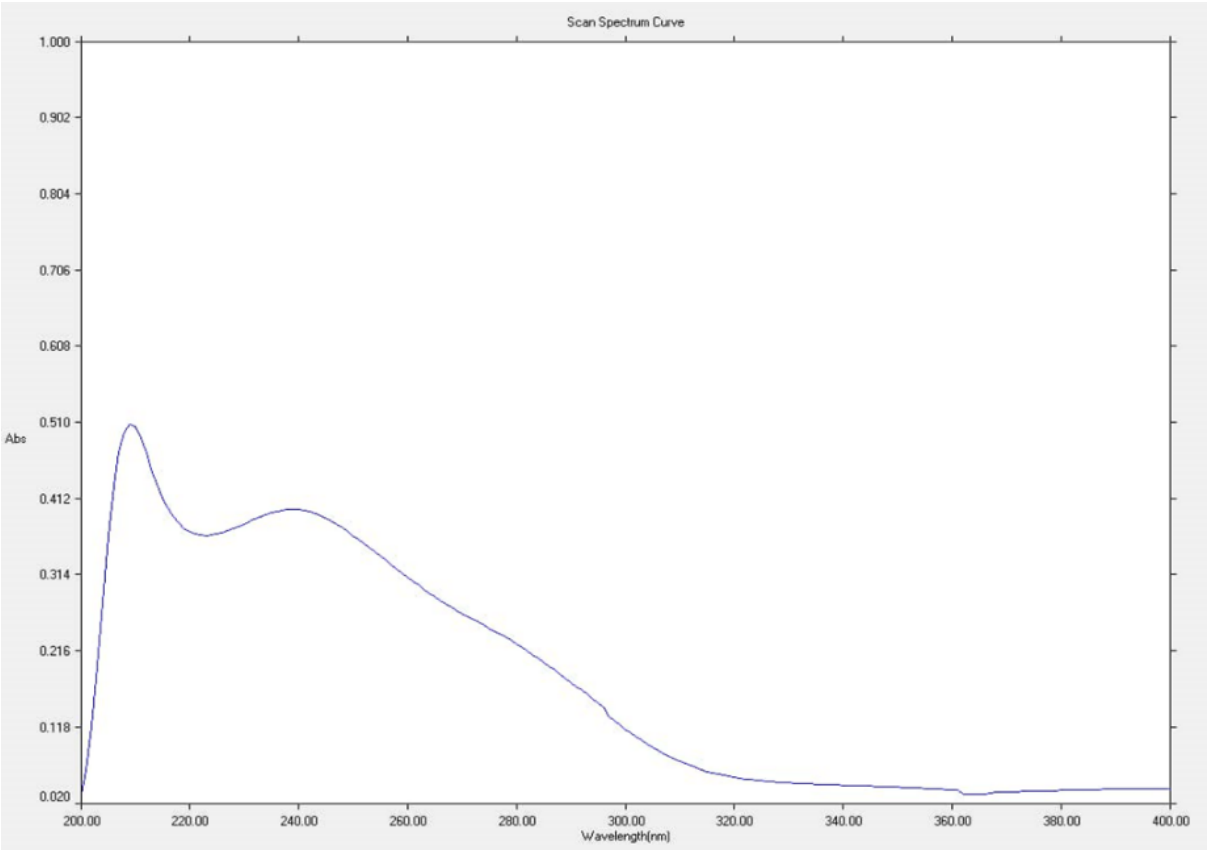


**Fig 1: UV absorbance of atorvastatin standard solution**

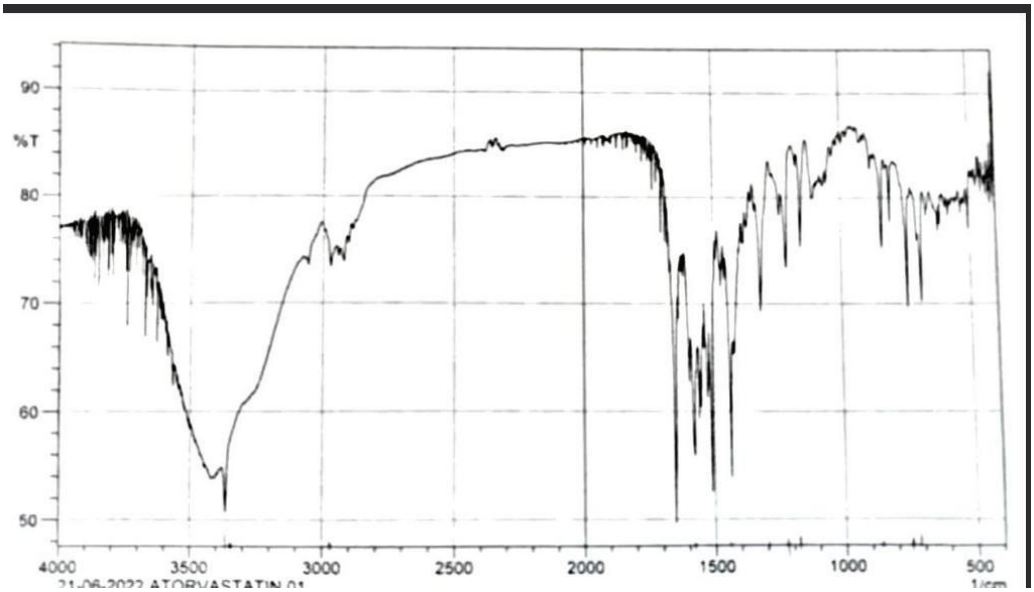


**Fig 2: FTIR spectrum of pure atorvastatin**

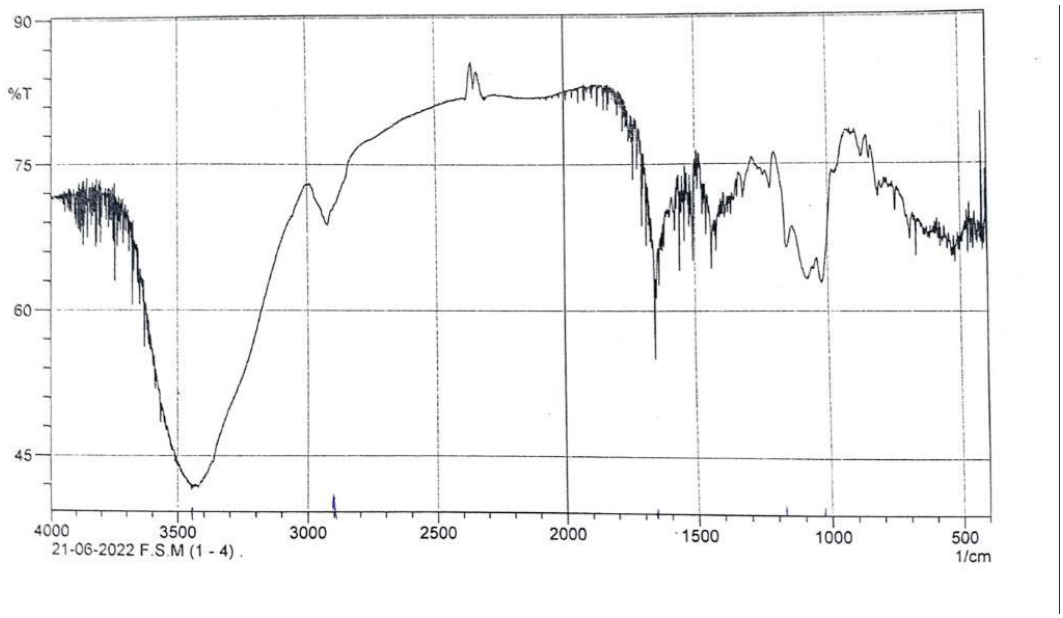


**Fig 3: FTIR spectrum of FSMSD**

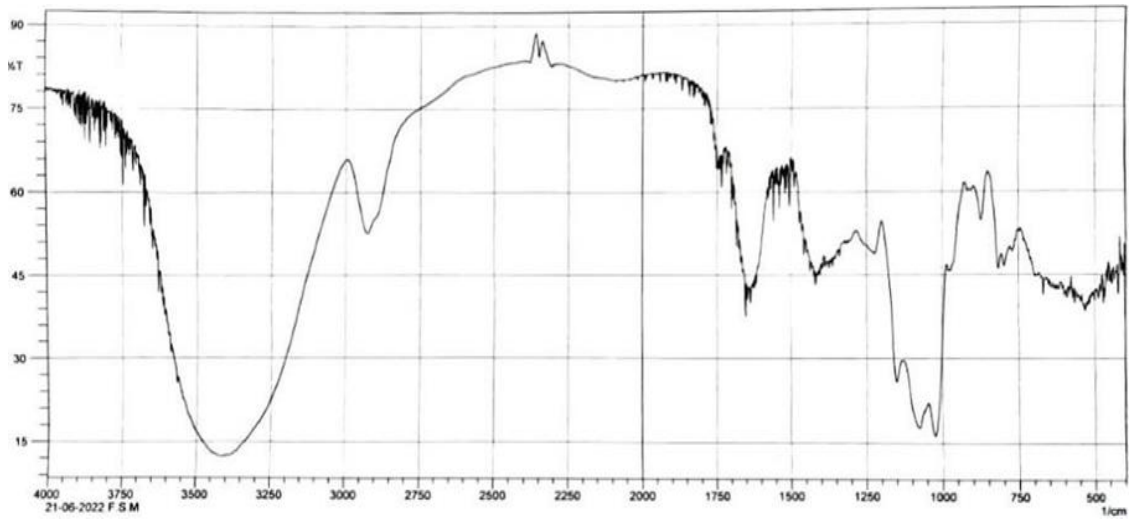


**Fig 4: FTIR spectrum of FSM**

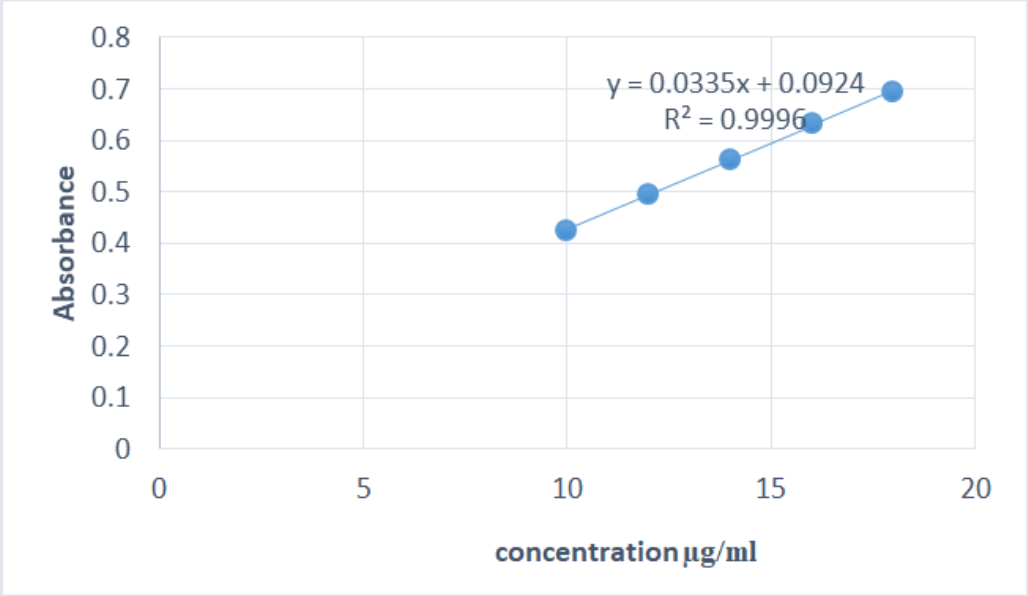


**Fig 5: Calibration curve of standard atorvastatin solution in water**

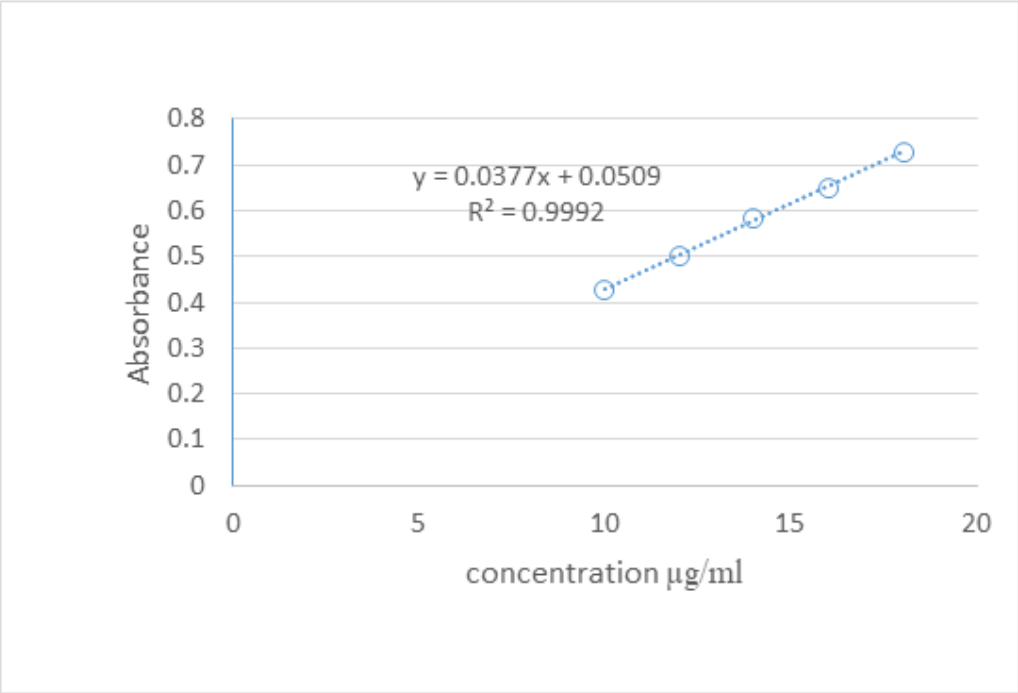


**Fig 6: Calibration curve of standard atorvastatin solution in phosphate buffer pH 6.8**

**Saturation solubility results:**

Saturation solubility of pure drug is 30.08 ± 0.37 µg /ml.

**Table-2: Concentration of saturated solutions of different preparations**

| | Ratio | FSM(µg /ml) | HPMC(µg /ml) |
|---|---|---|---|
| Solid dispersion | 1:2 | 60.37± 1.30 | 40.22± 1.27 |
| | 1:4 | 87.27± 1.25 | 51.73± 0.93 |
| | 1:6 | 95.31± 1.01 | 76.24± 1.11 |
| Physical mixture | 1:2 | 39.43± 0.36 | 35.39±0.93 |
| | 1:4 | 48.37± 0.75 | 43.52±0.87 |
| | 1:6 | 56.78± 0.35 | 57.32± 1.32 |

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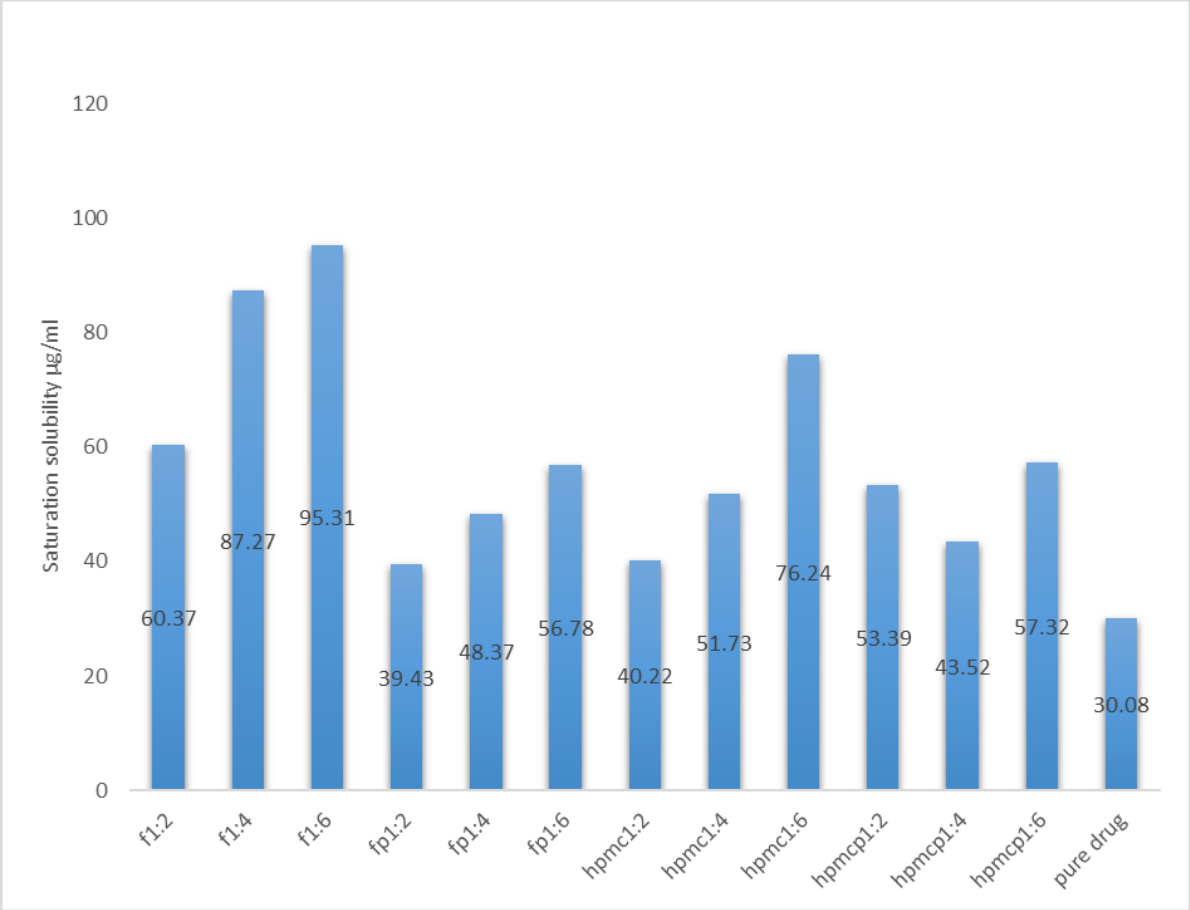


**Fig 7: Saturation solubility of pure drug and solid dispersions**

**Drug content determination:**

**Table-3: content percent of atorvastatin in the solid dispersions prepared:**

| Polymer | Ratio | Absorbance | Weight(mg) | Content % |
|---|---|---|---|---|
| FSMSD | 1:2 | 0.888 | 19.90 | 99.5 |
| | 1:4 | 0.891 | 19.96 | 99.8 |
| | 1:6 | 0.892 | 19.98 | 99.9 |
| HPMC | 1:2 | 0.890 | 19.95 | 99.8 |
| | 1:4 | 0.889 | 19.93 | 99.7 |
| | 1:6 | 0.890 | 19.90 | 99.5 |

**Table-4: Composition of the tablets**

| Ingredient | Quantity/ tablet (mg) | % |
|---|---|---|
| Solid dispersion | 140 | 40 |
| Lactose | 110 | 31 |
| Mcc | 80 | 23 |
| Primogel | 13 | 4 |
| Talc | 3.5 | 1 |
| Mg stearate | 3.5 | 1 |
| Distilled water | Qs | - |

**Table-5: Physiochemical properties of the tablets prepared**

| Average weight (gm ±SD) | Disintegration time (min) | Hardness test (Kg/cm$^3$) | Friability % | % Dissolved In 45 min |
|---|---|---|---|---|
| 0.3539 ± 0.0086 | 1.0 | 5.24 | 0.03 | 89 |

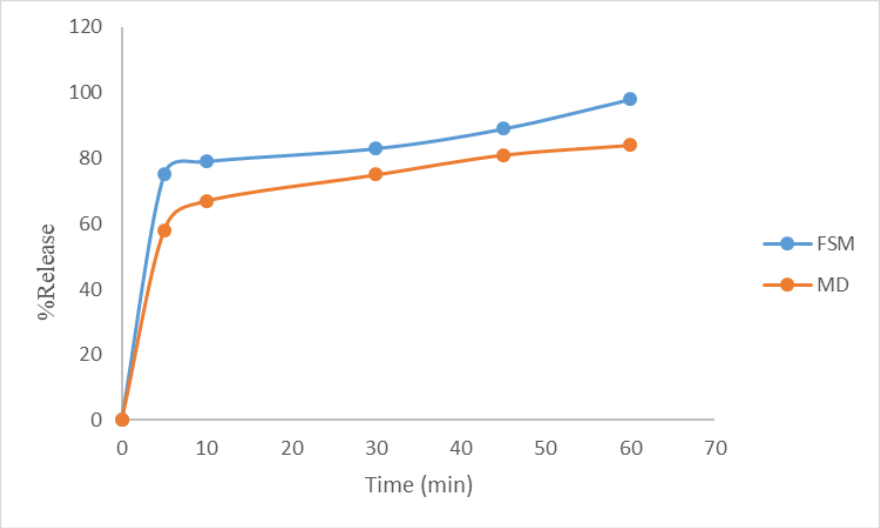


**Fig 8: Dissolution profile of FSMSD tablet and marketed drug(MD)**

## DISCUSSION

The aim of the present study was to enhance the solubility in order to increase oral bioavailability of atorvastatin as a BCS class II drug with low solubility and high permeability using fenugreek mucilage as natural polymer which is biocompatible, biodegradable, has low toxicity and relatively low production cost from abundant natural sources. These polymers degrade into biologically acceptable molecules that are metabolized and removed from the body through normal metabolic pathways [17].

The percentage yield of the mucilage was moderately low, which may increase the cost of the final product. So other method must be developed to increase and optimize the yield.

In the study, HPMC was used as a synthetic polymer that previously used in enhancing solubility of poor soluble drugs using solid dispersion techniques. Solid dispersions with different ratios of drug to polymer was prepared and compared to HPMC.

The prepared mucilage had good flow properties and poor compressibility which necessitate the use of wet granulation method in tablet preparation.

The FTIR spectra of Atorvastatin and atorvastatin FSMSD showed similar peaks which indicate that there were no interactions between atorvastatin and the polymer.

When testing saturation solubility, it was found that FSMSD with1:6 drug to polymer ratio had the highest saturation solubility compared to HPMCSD and physical mixtures of FSM with atorvastatin.

When calculating the drug content in the solid dispersions prepared it was founded that the dispersion contains the specified amount of the drug (from 99.2 to 100.1%). which is acceptable according to the United States Pharmacopeia [18].

The pH value of 1% solution of FSM was founded 6.1, which is nearly neutral and indicated that the polymer is non-irritating to the gastro-intestinal tract and can be used in tablet formulation safely.

The swelling index was found 10.2; which indicates good water absorption, and it can form a three dimensional network, from which the drug can be released through diffusion.

The physio-chemical properties of the tablet prepared were satisfactory according to the official guidelines. The disintegration of the tablets was very quick (1 min) which may indicate the disintegrating effect of FSM.

When conducting dissolution studies, the percent of drug released from the tablet after 45 min was 89% of the total drug, that indicates high rate of drug release from the dosage form.

## CONCLUSION

From the results above it concluded that:

- Solid dispersions with different drug to polymer ratios was prepared from FSM and HPMC using solvent evaporation method.
- FTIR spectroscopy test showed no evidence of interaction between the drug and the mucilage.
- Content percent of the drug in the solid dispersions prepared was found in the range accepted by the pharmacopeia (from 99.2 to 100.1%).
- Compared to pure drug, the saturation solubility of atorvastatin was increased by 2 folds (from 30 µg /ml for pure powder to 95 µg /ml for FSMSD with 1:6 drug to polymer ratio).

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- Drug release from the tablet after 45 min was 89%.

## RECOMMENDATIONS

- Further studies must be conducted to specify the disintegrating effect of FSM.
- In-vivo tests can be done to study the effect of solid dispersion in drug bioavailability.

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