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Pharmaceutical Sciences **Research Article……!!!**

SOLUBILITY ENHANCEMENT OF ATORVASTATIN CALCIUM BY USING SOLID DISPERSION TECHNIQUE AND FORMULATION OF FAST DISSOLVING TABLETS

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KEYWORDS:

Atorvastatin calcium, Solid dispersion, Fast dissolving tablets, *In vitro* dissolution studies.

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ABSTRACT

Atorvastatin calcium (ATC) is an oral anticholesteremic agent. ATC belongs to BCS class II drug having high permeability but low aqueous solubility. The major problem with this drug is its very low solubility in biological fluids, which results in poor bioavailability after oral administration. The solid dispersions of ATC with Guar gum and polyethylene glycol 4000 were prepared by using solvent evaporation method using different ratios with a view to increase its water solubility. The prepared solid dispersion showed improved solubility and dissolution rate as compared to pure drug. FTIR analysis showed no interaction between ATC, Guar gum and PEG 4000. The solid dispersions with PEG 4000 and Guar gum showed maximum drug release. Thus, SD4 and SD8 were incorporated into FDTs containing super-disintegrants (Crospovidone and sodium starch glycolate). The prepared tablets were evaluated for thickness, hardness, weight variation, friability, drug content, wetting time, water absorption ratio, disintegration time and *in-vitro* drug release. The drug release profile was studied in Phosphate buffer pH 6.8. Among all formulations F8 (containing Guar gum SD and crospovidone) showed a maximum of 88.52 % drug release in 10 min. F8 was subjected to stability studies. The formulation was found to be stable for two months at 40°C / 75% RH with insignificant change in the physical appearance and drug content.

INTRODUCTION:

Most of the new chemical entities (NCE) under development now-a-days are intended to be used as a solid dosage form that originates as an effective and reproducible route. But the fact is most NCEs are poorly water soluble drugs and the oral delivery of such drugs is frequently associated with low bioavailability and a lack of dose proportionality. Therefore improving dissolution is of great importance in order to ensure maximum therapeutic effect of these drugs. To overcome the problems associated with oral absorption and bioavailability issue, the solid dispersion (SD) technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble drugs because it is simple, economic, and advantageous.[1] It refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. A number of drugs have been shown to improve their dissolution character, when converted to solid dispersions.[2,3] Because of its poor aqueous solubility, Atorvastatin calcium posses dissolution related absorption problem. Hence, an attempt was made to improve the solubility of Atorvastatin calcium through solid dispersion technology and then formulating the fast dissolving tablets (FDTs).[4]

MATERIALS AND METHODS

Materials

Atorvastatin Calcium was obtained as gift sample from Theon pharmaceutics Pvt. Ltd, Sainimajra, Nalagarh, Solan (HP). Guar Gum, PEG 4000, Talc, Magnesium Sterate was obtained from SD Fine Chemicals, Mumbai. The Crospovidone, Sodium starch glycolate, microcrystalline cellulose wasb obtained from DFE Pharma, Banglore.

Formulation of Solid Dispersion (SD)

The SD was prepared by solvent evaporation method. Weighed amount of drug was dissolved in 20 ml of methanol. Then polymers (Guar gum and PEG 4000) were added in varying ratio's (D:P) 1:1, 1:2, 1:3, 1:4 respectively is shown in table 1. Methanol was completely evaporated by drying at 50°C for 5-25 min to obtain dry mass. The resultant mass was passed through 44 mesh sieve and stored in desiccators until used for further evaluation.[5]

Table 1: Formulation batches of Atorvastatin solid dispersion

Solid Dispersions	Ratio	Drug + Polymer
SD1	**1:1**	Atorvastatin calcium + PEG 4000
SD2	**1:2**	
SD3		
SD4	**1:3**	
	1:4	
SD5	**1:1**	Atorvastatin calcium + Guar Gum
SD6	**1:2**	
SD7	**1:3**	
SD8	**1:4**	

Evaluation of Solid Dispersion

Percentage yield

Thoroughly dried solid dispersion was collected and weighed accurately. The percentage yield was then calculated using formula given below.

$$\text{Percentage yield} = \frac{\text{Mass of solid dispersion obtained}}{\text{Total weight of drug and polymer}} \times 100$$

Estimation of drug content

Weighed quantity of SD equivalent to 10 mg of drug was added in 100 ml volumetric flask containing 5 ml of methanol. The material was mixed properly. The final volume was made up to 100 ml with phosphate buffer pH 6.8 and was spectrophotometrically analyzed at 241 nm.[6] The mean ± SD (standard deviation) values were calculated.

Fourier Transform Infrared Spectroscopy (FTIR)

The interference study was carried out using FTIR analysis. IR spectrum of pure drug and mixture of drug- polymer i.e. PEG 4000 and Guar Gum was performed for polymer drug interaction studies between 4000-400 cm-1 using KBr pellet method.

***In vitro* release studies of solid dispersion and pure drug (Atorvastatin)**

The *in vitro* dissolution study was carried out in the USP dissolution test apparatus type 2 (paddle). 900 ml of phosphate buffer pH 6.8 maintained at 37± 0.5°C was taken as the dissolution medium. The speed of the paddle was set at 50 rpm. 5 ml of the dissolution medium was withdrawn at selected time intervals (15, 30, 45, 60, 75, 90 min) and the same amount was replaced with the fresh medium. The withdrawn sample was filtered and analyzed by using UV spectrophotometer at 241 nm.[7] It was performed in triplicate.

Preparation of Fast Dissolving tablets (FDTs) containing Solid Dispersion by Direct Compression method

The SD formulation which showed maximum dissolution rate was selected to formulate FDTs. The SD equivalent to 10 mg of Atorvastatin calcium was taken. Then it was mixed with directly compressible diluents and superdisintegrants in the mortar pestle. Magnesium stearate and talc were passed through sieve no. 60 and mixed with the initial mixture in the mortar pestle followed by compression of the blend.[8] The formulation composition is shown in table 2.

Table 2: Formulation chart of FDTs containing solid dispersion

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
SD with PEG 4000 (1:4)	25	25	25	25	-	-	-	-
SD with Guar gum (1:4)	-	-	-	-	25	25	25	25
Sodium starch glycolate	3	5	-	-	3	5	-	-
Crosspovidone	-	-	3	5	-	-	3	5
Megnesium stearate	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2
Microcrysttaline Cellulose	68	66	68	66	68	66	68	66
Net weight (mg)	100	100	100	100	100	100	100	100

Evaluation of FDTs containing Atorvastatin SD

Evaluation of Pre-compression Parameters

The prepared powder blend was evaluated for various parameters like bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio. The results obtained are mentioned in table 3.

Angle of repose[9]

Angle of repose (θ) was determined by using funnel method. The blend was poured through a funnel. The funnel was raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured and angle of repose was calculated using formula:

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

where, θ = angle of repose of the blend, h = the height of heap and r = the radius of heap

Bulk density and tapped density[10]

10 g of the granules (W) were weighed and poured through funnel into a 100 ml measuring cylinder. The initial volume occupied by the sample was recorded. The cylinder was then allowed to fall under (tapped) its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. The bulk density and tapped density were calculated using formula:

$$\text{Bulk density} = W/Vo$$

$$\text{Tapped density} = W/VF$$

Where, W = weight of granules, V_0 = initial volume of the granules and V_F = final volume of the granules.

Compressibility index (Carr's index)[11]

The simplest way of measurement of free flow property of powder is compressibility, an indication of the ease with which material can be induced to flow is given by % compressibility which is calculated using formula:

$$C = (\rho t - \rho b) / \rho t \times 100$$

Where, ρt is tapped density and ρb is untapped density.

Hausner's ratio[11]

Hausner's ratio is an index of ease of powder flow. It is calculated by using formula:

$$\text{Hausner's ratio} = \rho t / \rho b$$

Where, ρt = Tapped density, ρb = Untapped density.

Evaluation of Post-compression Parameters[12, 13]

The prepared tablets were evaluated for post-compression parameters like weight variation, hardness, % friability, disintegration time, wetting time, dispersion time, drug content and dissolution studies. The results obtained are mentioned in table 4.

Weight variation: Twenty tablets were randomly selected from each batch and individually weighed. The average weight of these selected tablets was calculated.

Tablet thickness: The thickness of tablet was determined by using screw guage. Average thickness and standard deviation of each formulation was determined.

Hardness: The crushing strength or hardness of the tablets was measured using a Monsanto hardness tester. Three tablets from each formulation batch were tested randomly and the average reading was noted.

Friability: Friability of tablets was determined by using Roche Friabilator. Ten preweighed tablets were placed in chamber and subjected to 100 revolutions for 4 minutes. After these revolutions tablets were dedusted using a soft muslin cloth and reweighed. The friability was calculated by using formula:

$$F = (W_0 - W) / W_0 \times 100$$

Where, W_0 is the weight of tablets before test, W is the weight of the tablet after the test.

Wetting time and Water absorption ratio: A piece of tissue paper folded double was placed in a Petri plate (internal diameter 6.5 cm) containing 6ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. For measuring water absorption ratio, the weight of the tablet before keeping in a petridish was noted (w_b). The wetted tablet from the petridish was taken and reweighed (w_a). The water absorption ratio, R can be determined by using formula:

$$R = 100 (w_a - w_b) / w_b$$

***In vitro* dispersion time**

In vitro dispersion time was measured by dropping a tablet in a glass cylinder containing 50 ml Phosphate buffer pH 6.8. The time required for complete dispersion of tablets was measured and the mean ± SD (standard deviation) values were calculated.

% drug content determination

Five tablets were crushed in a glass mortar pestle. Then weight of powder equivalent to 10 mg Atorvastatin calcium was taken and dissolved in 100 ml of Phosphate buffer pH 6.8 in the volumetric flask. The flask was shaken for 4 h in a mechanical shaker. The solution was filtered

through whatmann filter paper and analyzed at 241 nm using a UV-visible double beam spectrophotometer. Each sample was analyzed in triplicate.

***In vitro* disintegration time**

Disintegration time of prepared tablets was determined in disintegration test apparatus. One tablet from each formulation was placed in each tube and the basket rack was positioned in a 1 litre beaker containing phosphate buffer pH 6.8 maintained at temperature 37± 2°C. The tablet should remain 2.5 cm below the surface of the liquid. The time taken for complete disintegration of the tablets with no particulate matter was noted and the mean ± SD (standard deviation) values were calculated.

***In vitro* Drug dissolution studies**

The dissolution profile of FDTs of atorvastatin was carried out in a beaker containing 30 ml of Phosphate buffer pH 6.8 as a dissolution medium, maintained at 37 ± 0.5°C. The medium was stirred at 100 rpm. Aliquots (5 ml) of the dissolution medium were withdrawn at 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 min time intervals and the same amount was replaced with the fresh medium. Samples were analyzed by using UV spectrophotometer at 241 nm. The percentage of the drug dissolved at various time intervals was calculated and plotted against time.

Stability Study[14]

The stability study of formulation (F8) was carried out at 40°C / 75% RH for two months. The tablets were wrapped in the aluminium foil and stored in a stability chamber at accelerated conditions. The drug content was checked at regular time intervals of 15, 30, 45 and 60 days respectively and was evaluated for physical appearance. The results of drug content are shown in table 5.

RESULTS AND DISCUSSION

Evaluation of Solid Dispersions

Percentage Yield

The yield obtained was in the range of 68.5-95.2%. The maximum percentage yield was obtained in SD4 and SD8 with 87.57% and 90.7% respectively.

Estimation of drug content

The drug content obtained was in the range of 90.13±0.18 to 96.24±0.37 %. Maximum drug content was obtained in SD4 and SD8 solid dispersion with 92.46±0.25% and 96.24±0.37% respectively.

Fourier Transform Infrared Spectroscopy (FTIR) It was observed that there is no interaction between drug and polymers shown in figure 1,2 and 3.

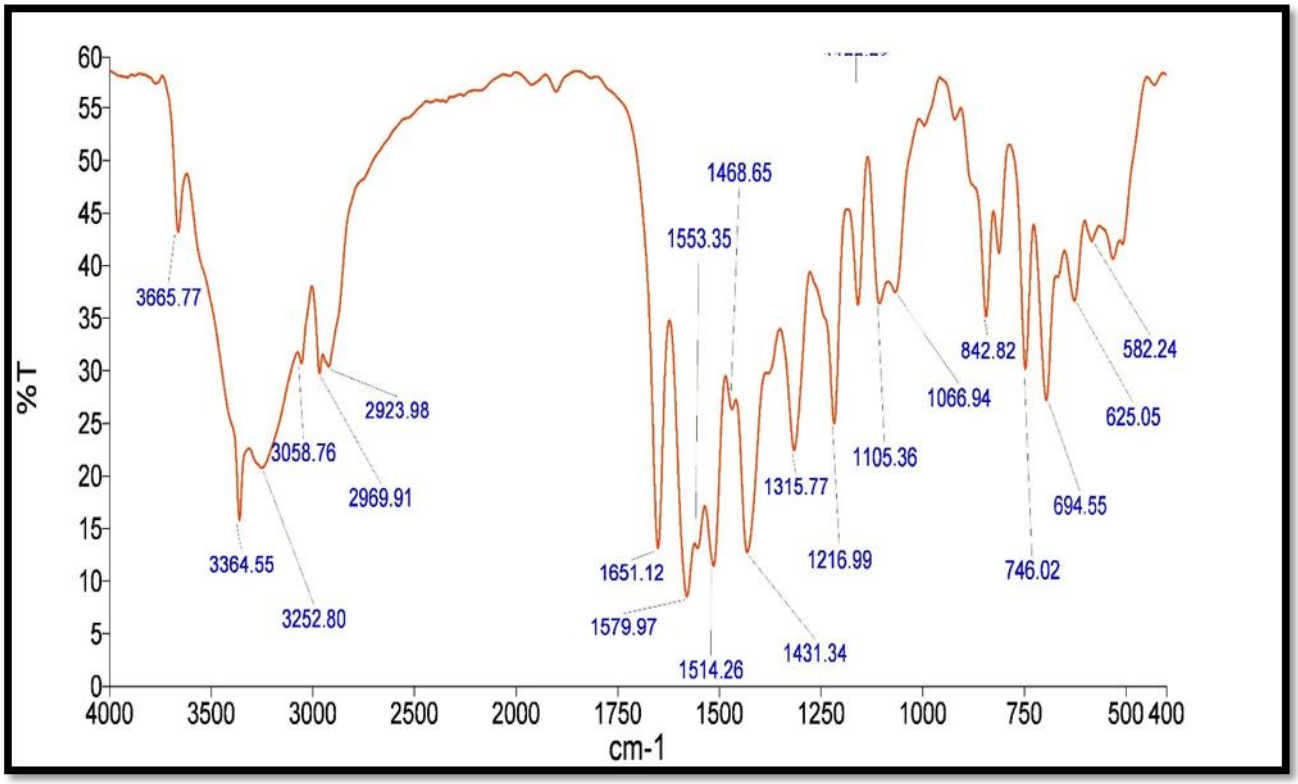

Figure 1: FTIR of Atorvastatin Calcium

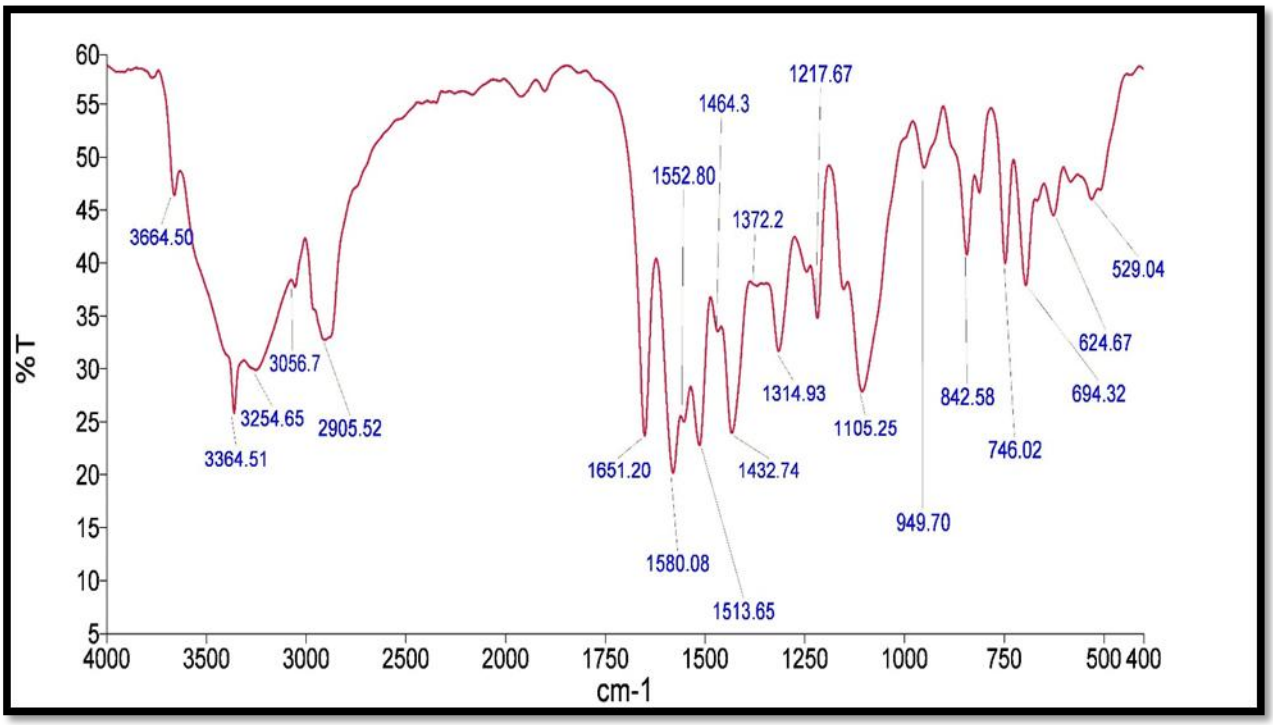

Figure 2: FTIR of Atorvastatin calcium with PEG 400

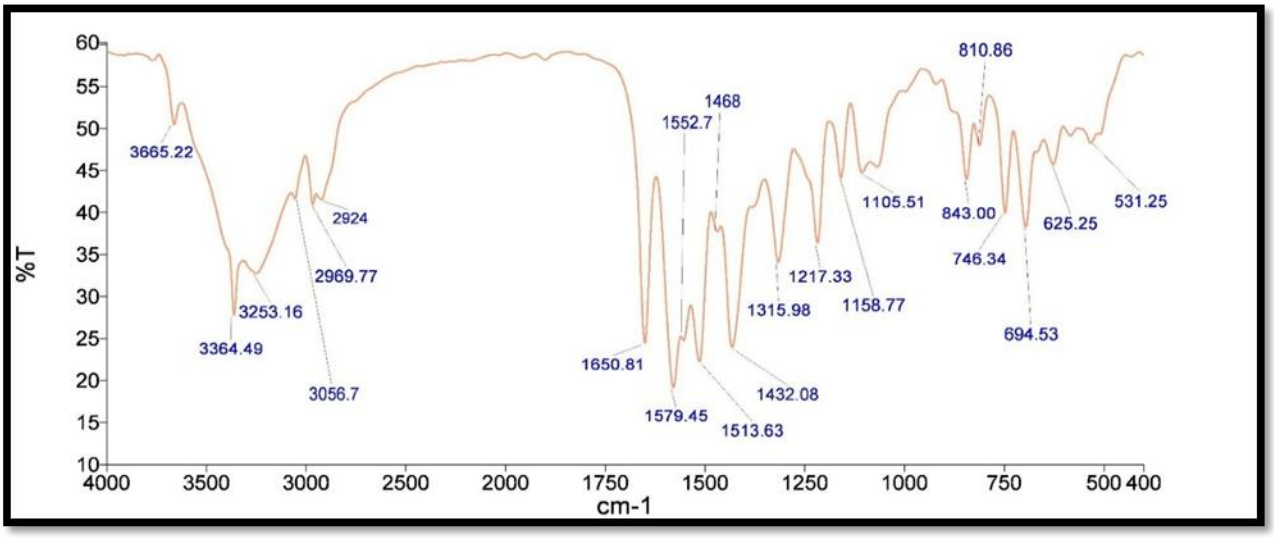

Figure 3: FTIR of Atorvastatin calcium with Guar Gum

***In vitro* release studies of solid dispersion and pure drug (Atorvastatin Calcium)**

From the data, it was observed that maximum amount of drug released was obtained in SD4 and SD8 solid dispersion with 75.43% and 83.32% respectively in 90 min, whereas the pure drug released maximum 26.45 % of drug in 90 min. The graph is shown in figure 4. Hence, formulations SD4 and SD8 were selected for further formulation study of Fast Dissolving Tablets.

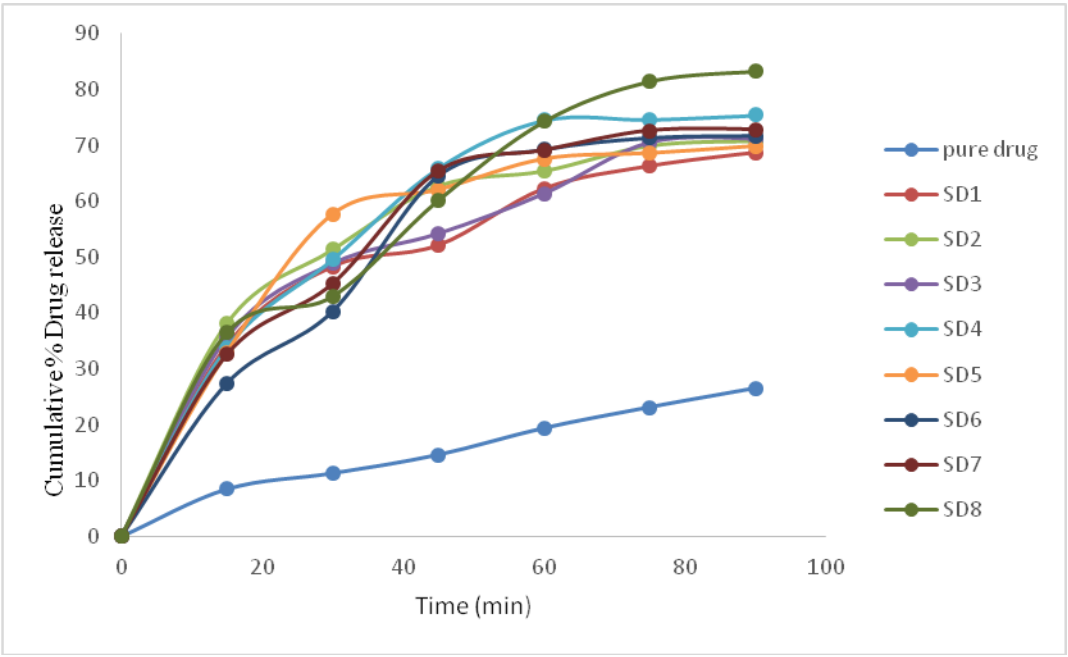

Figure 4: Cumulative % Drug Release of Atorvastatin calcium pure drug and SDs

Evaluation of FDTs containing Atorvastatin calcium SDs

Table 3: Data of Pre-compression parameters

Formulation code	Angle of Repose (θ) ±SD	Bulk Density (g/cc) ± SD	Tapped density (g/cc) ± SD	Carr's Index (%) ± SD	Hausner's Ratio ±SD
F1	22.10±1.21	0.47±0.01	0.55±0.02	14.5±1.05	1.17±0.02
F2	23.47±0.02	0.51±0.02	0.59±0.03	13.5±0.98	1.15±0.01
F3	23.11±0.01	0.53±0.01	0.61±0.01	13.1±0.61	1.10±0.03
F4	21.85±0.02	0.57±0.01	0.65±0.04	12.3±0.02	1.14±0.05
F5	22.41±0.73	0.48±0.07	0.57±0.01	15.7±1.35	1.18±0.08
F6	23.53±1.52	0.58±0.03	0.67±0.01	13.4±1.79	1.15±0.06
F7	22.51±0.78	0.54±0.02	0.62±0.02	12.9±1.81	1.14±0.04
F8	24.51±0.82	0.56±0.04	0.65±0.03	13.8±0.01	1.16±0.02

*All readings were in triplicate (n=3)

Table 4: Observation of post-compression parameters of FDTs

PARAMETER	F1	F2	F3	F4	F5	F6	F7	F8
Weight Variation test (mg) ±SD	99.58 ±0.91	99.35 ±1.09	98.05 ±1.33	98.47 ±0.39	97.37 ±1.30	99.28 ±0.72	98.16 ±0.81	98.96 ±0.93
Thickness (mm) ±SD	3.12 ±0.04	2.93 ±0.06	3.01 ±0.09	3.16 ±0.05	3.22 ±0.19	3.05 ±0.11	2.95 ±0.08	3.15 ±0.07
Hardness (kg/cm^2) ±SD	2.6 ±0.08	2.8 ±0.07	2.6 ±0.07	2.7 ±0.13	2.8 ±0.05	2.6 ±0.05	2.7 ±0.04	2.7 ±0.12
Friability (%) ±SD	0.31 ±0.06	0.24 ±0.07	0.28 ±0.05	0.19 ±0.03	0.32 ±0.04	0.30 ±0.06	0.23 ±0.08	0.30 ±0.05
Wetting time (sec) ±SD	35 ±0.56	29 ±0.85	34 ±0.63	26 ±0.81	27 ±0.92	37 ±0.52	32 ±0.78	24 ±0.96
Water absorption ratio (%) ±SD	66.35 ±1.25	72.12 ±1.31	84.28 ±0.47	81.13 ±0.18	68.32 ±0.50	75.21 ±0.45	88.74 ±0.68	83.27 ±0.28
In vitro dispersion time (sec) ±SD	24 ±0.14	23 ±0.12	26 ±0.05	21 ±0.11	22 ±0.11	23 ±0.15	25 ±0.04	20 ±0.02
Disintegration time (sec) ±SD	43 ±0.62	38 ±0.85	35 ±0.49	38 ±1.67	32 ±0.68	29 ±1.23	44 ±1.02	24 ±0.72
% Drug content (%) ±SD	96.02 ±0.12	97.26 ±0.37	96.72 ±0.28	97.32 ±0.02	97.41 ±0.11	96.35 ±0.16	96.52 ±0.18	97.53 ±0.01

SD= Standard deviation

***In vitro* Drug dissolution studies**

From the data, formulation F8 released 88.52 % of drug in 10 min. On the basis of drug release, formulation F8 containing crospovidone as superdisintegrant released drug at a faster rate.

Therefore, formulation F8 was selected as the best formulation. The graph between cumulative % drug release versus time is shown in figure 5.

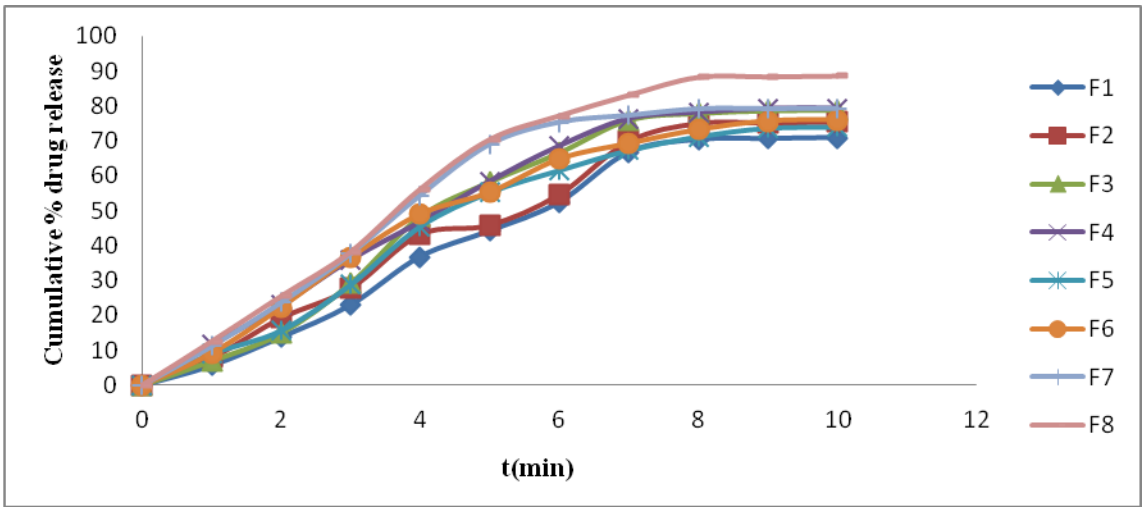

Figure 5: Graph showing Cumulative % Drug Release from FDTs

Stability Study

There was no significant change in physical appearance, Drug content at the end of two months and the results of drug content is shown in table 5.

Table 5: Drug Content data during Stability Study

Time (days)	Accelerated conditions (40± 2^0C / 75 ± 5% RH)	
	Physical Appearance	Drug Content
0	+	97.53±0.03
15	+	96.54±0.17
30	+	96.33±0.04
45	+	95.32±0.11
60	+	95.09±0.06

(+) indicates no change in physical appearance

CONCLUSION

In the present research work, an attempt was made to formulate fast dissolving tablets of Atorvastatin Calcium (ATC). As ATC is a BCS Class II drug with low solubility and high permeability. Therefore, the solid dispersions were prepared to improve the solubility of the drug. They were prepared by solvent evaporation method using two different polymers i.e. Guar Gum and PEG 4000. On the basis of dissolution studies SD4 and SD8 solid dispersions were selected for

tableting. Eight formulations of fast dissolving tablets were prepared. All the formulations F1 to F8 were subjected to *in vitro* release studies and formulation F8 showed maximum release 88.52 % of drug in 10 min.

REFERENCES

1. Bess WS, Kulkarni N, Ambike SH and Ramsay MP, (2006), Fast Dissolving Orally Consumable Solid Film containing a Taste Masking Agent and Pharmaceutically active agent, US Patent 7067116.
2. Huda N.H., Saffoon N., Sutradhar K.B., Uddin R.. Enhancement of Oral Bioavailability and Solid Dispersion: A Review. J App Pharm Sci.2011;1:13-20.
3. Baghel R.S., Singh S., Yadav L.. A review on solid dispersion. Int J of Pharm & Life Sci.2011;2:1078-1095.
4. Rajitha K, Shravan kumar Y, Adukondalu D, Ramesh Gannu, Madhusudan Rao Y. Formulation and evaluation of orally disintegrating tablets of buspirone. Int. J. Pharm. Sci. 2009;1(4):327 - 334.
5. Uchino T,Yasuno N, YanagilharaY, Suzuki H. Solid dispersion of spironolactone with porous silica prepared by the solvent method.Pharmazie 2007;62:599-603.
6. Onyeji CO, Omoruyi SI, Oladimeji FA, Soyinka JO. Physicochemical characterization and dissolution properties of binary systems of pyrimethamine and 2- hydroxypropyl β–cyclodextrin. Afr J Biotechnol 2009;8:1651-659.
7. Veiga F, Teixeirra D, Kedzeirewicz F, Sousa A and Maincent P. Inclusion complexation of tolbutamide with β-cyclodextrin and hydroxylpropyl- β-cyclodextrin. Int. J. Pharm. 1996;129(1):63-71.
8. Rajitha K, Shravan kumar Y, Adukondalu D, Ramesh Gannu, Madhusudan Rao Y. Formulation and evaluation of orally disintegrating tablets of buspirone. Int. J. Pharm. Sci. 2009;1(4):327-334.
9. RG Alfonsa. Remington's pharmaceutical sciences.18 ed, Maryland: Lippincot and wilkins.1990:1677-678.
10. The United States Pharmacopoeia-National Formulary. 2009 ed, Rockville: The United States Pharmacopoeial Convention. 2009;1:226-27.
11. Lachman L, Liberman HA, Kanig JL. The theory and practice of industrial pharmacy. 3rd ed. Bombay;Varghese publishing house 1987.
12. The Indian Pharmacopoeia. Vol II. New Delhi;The controller of publications 1996.

13. Rockville MD. The United State Pharmacopoeia. 24th Asian ed. United state pharmacopoeial convention Inc 2000.

14. Prabhu H, Rajanna G, Anita D. Development of mouth dissolving tablets of cinnarazine. Int J Pharm Sci 2010;2:631-40.