ORIGINAL ARTICLE

Formulation and Evaluation of Atorvastatin Fast Dissolving Tablets using *Entada scandens* Seed Starch as Superdisintegrant

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Abstract

Aim: The purpose of the present work was to formulate fast dissolving tablets (FDTs) of poorly water-soluble drug Atorvastatin using natural superdisintegrants like starches extracted from *Entada scandens* seed powder. **Objectives:** The present work mainly focuses on solubility enhancement of BCS Class-II drugs using starch as superdisintegrant which improves drug release. **Materials and Methods:** Starches were extracted using alkali method, i.e., sodium hydroxide at 0.1%, 0.25%, and 0.5% concentrations and water from *E. scandens* seed powder. These starches were evaluated for various phytochemical, physicochemical tests, and acute toxicity studies. FDTs were prepared using Atorvastatin, Starch, and Croscarmellose sodium (CCS) in various concentrations using wet granulation technique. Various pre- and post-compression parameters were performed along with *in vitro* drug release studies, characterization studies such as Fourier transform infrared (FTIR), differential scanning calorimetry (DSC), scanning electron microscopy, X-ray diffraction (XRD), and stability studies. **Results and Discussion:** Phytochemical tests revealed the presence of only starch in all the extracts. Acute toxicity studies indicated the healthy condition of all mice. The starch prepared from 0.5% sodium hydroxide (*E. scandens* seed starch [ESS4]) showed best physicochemical properties. From *in vitro* dissolution studies, it was observed that formulations F5 and F11 containing 15% w/w of ESS4 and 15% w/w of CCS showed faster disintegration and enhanced dissolution rate compared with other formulations. FTIR and DSC studies revealed that there were no major interactions between the drug and excipients. XRD studies revealed the nature of formulations. Accelerated stability studies revealed that all tablets were stable. **Conclusion:** Thus, the tablets prepared using ESS4 revealed the superdisintegrant property of starch.

Key words: Atorvastatin, croscarmellose sodium, *Entada scandens*, fast dissolving tablets

INTRODUCTION

Although drug administration can be done in various routes, oral route is widely preferred due to its ease. However, it is difficult in some cases such as in geriatrics and children to swallow drug. To reduce such difficulties, fast dissolving tablets (FDTs) are developed. These tablets when comes in contact with saliva in mouth; they rapidly disintegrate and releases drug.[1] FDTs are highly acceptable due to their advantage such as patient compliance, rapid action, enhanced bioavailability, and quick disintegration.[2] Mostly these are prepared using a wet granulation technique. Usage of certain superdisintegrants such as sodium starch glycolate, croscarmellose, and polyvinylpyrrolidone provides instantaneous degradation of tablets. They are effective even at low concentrations. They are added to the tablet and some encapsulated formulations to promote the breakup of tablet and capsules "slugs" into smaller fragments in an aqueous environment thereby increasing the available surface area and promoting a more rapid release of the drug substance. They promote moisture penetration and dispersion of the tablet matrix.[3]

Natural superdisintegrants are preferable over synthetic forms, due to their abundant availability, cheaper in cost,

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non-irritating, and non-toxic in nature. Several gums and mucilages have superdisintegrant property. These are mainly useful in enhancing the water solubility of BCS Class-II drugs. These are the drugs with low solubility and high permeability properties. Past studies revealed the applications of components from plants such as *Ocimum tenuiflorum*, *Plantago ovata* mucilage, *Aloe vera* mucilage, mucilage of *Hibiscus rosasinesis,* and Lotus bean gum as superdisintegrants in formulating several BCS Class II drugs.[4]

In the present study, an attempt was made to extract starch from of *Entada scandens* seed powder and to use it as superdisintegrant for formulating FDTs. The seed starch obtained from *E. scandens* possess superdisintegrant property. *E. scandens* which belongs to the family Fabaceae, grows in evergreen tropical climates of India, Africa, and Australia. Fruits grow up to 6 m length with many seeds. Their seeds have a thick and durable seed coat which is brownish in color, which allows them to survive lengthy periods of immersion in seawater. It contains a fleshy white cotyledon. These are rich in starch contents.[5] Atorvastatin which is an antihyperlipidemic agent is selected as the drug of choice for the present study. It belongs to the statins class which mainly acts by inhibiting the hepatic enzyme HMG-CoA reductase. This prevents the conversion of HMG-CoA to mevalonate in cholesterol biosynthesis. The absolute bioavailability of Atorvastatin is approximately 14%. The systemic availability for HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic bioavailability is due to pre-systemic clearance by gastrointestinal mucosa and first-pass metabolism in liver. More than 98% of the drug is bound to plasma proteins. It has an approximate elimination half-life of 14 h.[6] Based on pharmacokinetic and pharmacodynamic parameters, Atorvastatin is selected as drug of choice for the present study.

MATERIALS AND METHODS

Materials

Atorvastatin was a gift sample from Mylan Laboratories Ltd. (Hyderabad, India). Sodium hydroxide, magnesium stearate, and talc were procured from S.D Fine Chem. Ltd. (Mumbai, India). Isopropyl alcohol was obtained from High Pure Fine Chem. (Chennai, India); croscarmellose sodium (CCS) was a gift from M/S NATCO Pharma Ltd. (Hyderabad, India), and *E. scandens* seeds were procured from the local market (Kurnool, Andhra Pradesh, India).

Extraction of starch from *E. scandens* seeds

E. scandens seed starch (ESS4) was isolated using aqueous and alkali extraction methods.[7] 5 g *E. scandens* seed flour was added into 100 ml distilled water, 0.1%, 0.25%, and 0.5% sodium hydroxide solutions separately and soaked (6 h and 8 h) at room temperature then stirred constantly. The slurry was filtered through 212 mesh stainless sieve, and remaining sediment was washed with distilled water for 3 times. The filtrates were combined and precipitated overnight at 4°C. The supernatant was discarded, and the crude starch was cleaned with distilled water. This step was repeated 3 times, and the starch cake was dried at 40°C for 24 h in oven dryer. The starch was ground with a mortar and pestle. The starches were packed in a plastic bag and kept at room temperature until further use.

Phytochemical tests for *E. scandens* seed powder and extracted starches

The raw *E. scandens* seed powder and starches extracted were subjected to various phytochemical tests for identification of carbohydrates, proteins, alkaloids, glycosides, steroids, flavonoids, and saponins.[8] The results were indicated in Table 1.

Evaluation of physicochemical properties of *E. scandens* seed powder and extracted starches

Various physicochemical properties were evaluated using suitable methods.[8]

Gelatinization temperature

Samples of starch powder were moistened with water and loaded into capillary tube by means of intrusion. The

Table 1: Phytochemical screening of *Entada scandens* seed powder and starches

Test	ESSP	ESS1	ESS2	ESS3	ESS4
Carbohydrates	+	+	+	+	+
Polysaccharides	+	+	+	+	+
Proteins	+	–	–	–	–
Alkaloids	+	–	–	–	–
Glycosides	–	–	–	–	–
Steroids	+	–	–	–	–
Flavonoids	+	–	–	–	–
Saponins	+	–	–	–	–

+: Indicates present, –: Indicates absent

temperature of gelling and the time from swelling to full gelatinization was measured with a melting point apparatus. The results were given in Table 2.

Determination of pH

The pH values of 1% solutions were measured using a digital pH meter. The results were given in Table 2.

Viscosity

Flow property of a simple liquid is expressed in terms of viscosity. Viscosity is an index of resistance of a liquid to flow. The higher the viscosity of a liquid, the greater is the resistance to flow. The viscosity was measured using a brook field viscometer. The results were given in Table 2.

Swelling index

1 g of powdered mucilage was treated with 25 ml of water in a graduated cylinder shaken for every 10 m for 1 h and allowed to stand as specified. The results were shown in Table 2.

Swelling index = Weight of wet mass/Weight of dry powder × 100

Water absorption index

1 g of sample was suspended in 10 ml of distilled water at 30°C in a centrifuge tube, stirred for 30 m intermittently and then centrifuged at 3000 rpm for 10 m. The supernatant was decanted, and the weight of the gel formed was recorded. The water absorption index was then calculated as gel weight per gram dry sample. The results were given in Table 2.

Water absorption Index = Bound water (g)/Weight of sample (g) × 100

Total microbial load of isolated *E. scandens* starch

The total microbial load is an important parameter which decides the suitability of a substance for use as an excipient in the pharmaceutical dosage form. The starch powders were subjected to dry heat sterilization at 180°C for 30 min. Then, the starches were inoculated on medium and were incubated for 24 h. Then, the colonies were counted using a microbial colony counter.

Acute toxicity studies of ESS4 on albino mice

Twenty-five adult male Albino Mice were procured from Mahaveer Enterprises (Hyderabad, India) and were housed five per each cage 7 days before experiment period under ideal environment as per Organization for Economic Cooperation and Development guidelines. Animals were weighed before dose administration. Five groups containing a total of 25 albino mice (25–50 g) were used in the study. All animals were fed orally once with different doses of starch (100 mg/kg, 500 mg/kg, 1000 mg/kg, and 2000 mg/kg body weight) to different groups (Groups I, II, III, and IV) of animals. The control group of animals received an only saline solution. After the experimental protocol is completed, the animals were kept under ambient conditions. All animals were kept under continuous observation after the administration of the dose for any change in behavior or physical activities.[9] The results are given in Table 3.

Table 2: Physicochemical properties of *Entada scandens* seed powder and extracted starches

Properties	ESSP	ESS1	ESS2	ESS3	ESS4
Gelatinization temperature	118–121°C	120–123°C	122–126°C	124–127°C	126–129°C
pH	6.32	6.50	6.62	6.78	6.98
Viscosity	1.856 cps	2.089 cps	2.166 cps	2.265 cps	2.312 cps
Swelling index	58	63	84	76	78
Water absorption index	Less	More	More	More	More
Total microbial Load	Absent	Absent	Absent	Absent	Absent

Table 3: Acute toxicity studies in male albino mice

Group	Dose (mg/kg body weight)	Mortality (x/N)	Symptoms
Control	----	0/5	Normal
I	100	0/5	Normal
II	500	0/5	Normal
III	1000	0/5	Normal
IV	2000	0/5	Corner sitting and salivation

Formulation of atorvastatin FDTs

Atorvastatin FDTs were prepared by wet granulation technique. Isopropyl alcohol was used as the granulating fluid. The FDT formulations consisted of drug, superdisintegrants, and excipients. The weight of all FDT formulations was maintained uniformly using microcrystalline cellulose as diluent.

FDT formulations were formulated using various concentrations of ESS4 extracted by water and alkali and CCS. In total, the tablet formulations consisted of drug, superdisintegrants, and excipients. The drug concentration was maintained constant while ESS4 and CCS concentrations were varied. The compositions of various tablet formulations were given in Table 4. The raw materials were individually weighed and were then converted into damp mass using isopropyl alcohol. The damp mass was passed through sieve no 20 to obtain granules, and they were kept for drying. The prepared granules were passed through sieve no. 40. The granules were taken into a plastic bag and lubricated with 1% talc, magnesium stearate, and half of the starch. Then, they were compressed as tablets using CLIT 10 station mini press. To minimize the processing variables, all batches of tablets were compressed, under identical conditions.

Evaluation of pre-compression parameters

The prepared granules were evaluated for pre-compression parameters such as angle of repose, Carr's index, and Hausner's ratio.[10] The results were given in Table 5.

Angle of repose

The powder flow properties were determined to know the good or bad material flow by conducting this process in which powder is taken into a funnel through which the powder to be calculated to its angle of repose is poured through funnel below this graph sheet is placed and allowed it to flow during this process material will form a heap like structure for which we can measure its radius and its height of the heap using the formula.

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

This is a simple index that can be determined on small quantities of powders.

Carr's index

A simple test was used to evaluate the flowability of a powder by comparing the poured density and the tapped density of a powder and the rate at which it is packed down.

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{poured density}}{\text{Tapped density}} \times 100$$

Hausner's ratio

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

Hausner's ratio = Tapped density/Bulk density

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Evaluation of post-compression parameters

The compressed tablets were further evaluated for post-compression parameters such as weight uniformity, hardness,

Table 4: Composition of various atorvastatin fast dissolving tablets with different superdisintegrant concentrations

Ingredient mg/tablet	Formulations										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Atorvastatin	10	10	10	10	10	10	10	10	10	10	10
MCC PH 102	226.25	220	213.75	207.50	195	232.5	226.25	220	213.75	207.50	195
ESS4	6.25	12.50	18.75	25	37.5	-----	-----	-----	-----	-----	-----
CCS	-----	-----	-----	----	-----	-----	6.25	12.50	18.75	25	37.5
Saccharin Sodium	5	5	5	5	5	5	5	5	5	5	5
Isopropyl alcohol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Lemon flavor	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Talc	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Magnesium stearate	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Total weight	250	250	250	250	250	250	250	250	250	250	250

CCS: Croscarmellose sodium

friability, wetting time, dispersion test, and drug content.[11] The results were given in Table 6.

Weight uniformity

A total of 20 tablets were selected randomly from a batch and were individually weighed and then the average weight was calculated. The weights of individual tablets were then compared with the average weight that was already calculated. The tablets meet the specifications if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limits.

Hardness

The crushing Strength/Hardness which is the force required to break the tablet in the radial direction was measured using a Monsanto hardness tester (Tab-machines, Mumbai). The tablet to be tested is held in fixed and moving jaw and reading of the indicator adjusted to zero. Then, force to the edge of the tablet was gradually increased by moving the screw knob forward until the tablet breaks. The reading was noted from the scale which indicates the pressure required in kg/cm^2 break the tablet.

Friability

Friability test was performed using Roche friabilator (REMI Equipment, Mumbai). 10 tablets of a batch were weighted and placed in a friabilator chamber, and it was allowed to rotate for 100 revolutions. During each revolution, these tablets fall from a distance of six inches to undergo shock. After completion of 100 revolutions, tablets were again weighed, and the loss in weight indicated friability. The acceptance limits of weight loss should not be more than 1%. This test was performed to evaluate the ability of the tablets to withstand abrasion in packing, handling, and transporting.

Wetting time

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water or phosphate buffer pH 6.8, a tablet was put on the paper and the time for complete wetting was measured. Less wetting time indicates high porosity of the tablets.

Dispersion test

It is an assessment of the grittiness which arises due to the disintegration of the tablet into coarse particles. The test is performed by placing two tablets in 100 ml water and stirring it gently for 3 min and pass through 22 mesh. The formulation is considered to form a smooth dispersion if the complete dispersion passes through a sieve screen with a nominal mesh aperture of 710 μm (sieve no. 22) without leaving any residue on the mesh.

Table 5: Pre-compression parameters of prepared granules of various fast dissolving tablet formulation

Formulation	Angle of repose (°)	Carr's index (%)	Hausner's ratio
F1	25	16	1.14
F2	26	12	1.19
F3	30	12	1.15
F4	25	14	1.14
F5	30	15	1.15
F6	30	12	1.14
F7	24	15	1.16
F8	27	14	1.15
F9	29	15	1.19
F10	28	13	1.14
F11	25	14	1.15

Table 6: Post-compression parameters of various atorvastatin fast dissolving tablet formulations

Formulation	Weight uniformity (mg)	Hardness (kg/cm^2)	Friability (% loss)	Wetting time (s)	Dispersion time (s)	Drug Content (mg tablet)
F1	250±2	3.0±0.5	0.3	140	Passed	9.64±0.5
F2	251±2	3.5±0.3	0.2	120	Passed	9.90±0.4
F3	250±1	3.0±0.5	0.2	90	Passed	9.82±0.3
F4	248±3	3.2±0.4	0.2	70	Passed	10.79±0.6
F5	250±3	3.5±0.2	0.4	60	Passed	9.52±0.2
F6	249±2	3.2±0.4	0.2	220	Passed	9.96±0.6
F7	250±2	3.0±0.5	0.3	146	Passed	10.34±0.3
F8	251±1	3.2±0.8	0.4	130	Passed	9.74±0.4
F9	248±3	3.2±0.4	0.3	100	Passed	10.10±0.2
F10	250±2	3.5±0.1	0.2	85	Passed	10.10±0.2
F11	248±1	3.2±0.3	0.3	65	Passed	9.32±0.4

Drug content uniformity

FDTs of Atorvastatin from a batch were taken at random and were crushed to a fine powder. The powdered material was transferred into a 100 ml volumetric flask, and few ml of methanol was added to it. It was shaken occasionally for about 30 min, and the volume was made up to 100 ml by adding methanol. The resulting solution was set aside for few minutes, and the supernatant solution was collected, filtered by using Whatman filter paper. Then, the filtrate was subsequently diluted with phosphate buffer pH 6.8, and the absorbance was measured at 243 nm. This test was repeated 6 times ($n = 6$) for each batch of tablets.

In vitro dissolution studies of atorvastatin FDTs

Dissolution studies for each tablet formulation were performed in a calibrated 8 station dissolution test apparatus (LABINDIA DS8000) equipped with paddles (USP apparatus II method) employing 900 ml of phosphate buffer pH 6.8 as a dissolution medium. The paddles were operated at 50 rpm, and temperature was maintained at 37 ± 1°C throughout the experiment. The samples were withdrawn at 5, 10, 15, 20, 30, 45, and 60 min and replaced with equal volume of the same dissolution medium to maintain the constant volume throughout the experiment. Samples withdrawn at various time intervals were suitably diluted with same dissolution medium, and the amount of the drug dissolved was estimated by Lab India double beam U.V spectrophotometer (UV 3000+) at 243 nm. The dissolution studies on each formulation were conducted in triplicate. The dissolution profiles for all formulations were given in Tables 7–8 and shown in Figures 1-2.

Characterization studies

Based on the dissolution studies, the optimized formulations were selected, and Fourier transform infrared (FTIR) and differential scanning calorimetry (DSC) studies were performed to observe the drug-polymer interactions. X-ray diffraction (XRD) studies were performed to detect the nature of formulations. Scanning electron microscopy (SEM) analysis was performed on *E. scandens* seed powder, ESS4, Atorvastatin, a blend of Atorvastatin with ESS4, and a blend of Atorvastatin with CCS to know surface characteristics. The results were shown in Tables 3-6.

Stability studies

Accelerated stability studies were carried out on optimized formulations (F5 and F11) as per International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines. After the

Table 7: Dissolution profiles of atorvastatin FDTs prepared by wet granulation method (F1–F6)

Time (min)	Cumulative % drug released					
	F1	F2	F3	F4	F5	F6
5	54.12	55.38	59.160	60.41	70.80	50.97
10	65.45	66.71	67.34	68.28	84.26	61.04
15	67.97	69.54	70.17	74.58	93.04	65.13
20	70.80	72.69	73.63	80.20	97.50	68.28
30	74.26	75.52	77.09	87.72	98.07	70.80
45	76.78	77.41	77.72	89.18	98.52	71.63
60	78.35	78.98	79.92	92.44	98.65	71.89

FDTs: Formulate fast dissolving tablets

Table 8: Dissolution profiles of atorvastatin FDTs prepared by wet granulation method (F6–F11)

Time (min)	Cumulative % drug released					
	F6	F7	F8	F9	F10	F11
5	50.97	53.49	54.75	56.95	60.41	60.73
10	61.04	61.99	63.25	61.99	67.97	70.80
15	65.13	65.76	66.71	67.65	74.74	83.63
20	68.28	68.91	70.80	72.06	81.58	90.15
30	70.80	72.06	73.32	73.95	86.15	95.04
45	71.63	74.58	75.52	76.46	91.72	97.93
60	71.89	75.83	76.78	78.04	92.67	98.18

FDTs: Formulate fast dissolving tablets

stability studies, the formulations were evaluated for physical parameters, drug content, and drug release studies. The results were indicated in Table 9.

RESULTS AND DISCUSSION

Extraction of starch from *E. scandens* seeds

E. scandens seed powder made through prescribed procedure was subjected to extraction of starch by aqueous and alkali extraction processes. The starch thus obtained by different extraction processes were dried at ambient conditions for 24 h. The starches thus obtained were crisp slightly granular, free-flowing, and stable in nature. Further, these starches were evaluated for phytochemical studies as per the procedures mentioned in the methods.

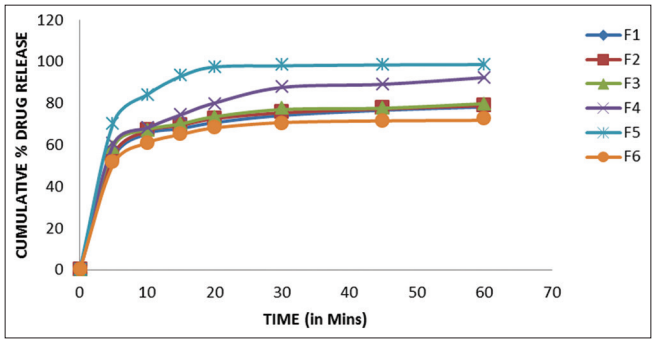

Figure 1: Drug release profiles of atorvastatin fast dissolving tablets prepared by wet granulation method (F1–F6)

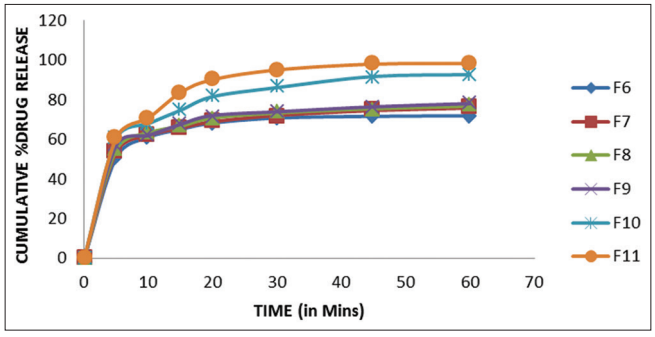

Figure 2: Drug release profiles of atorvastatin fast dissolving tablets prepared by wet granulation method (F6–F11)

Phytochemical screening of *E. scandens* seed flour and starch extracts

The raw *E. scandens* powder and starches extracted from it were for the presence of carbohydrates, polysaccharides, proteins, alkaloids, glycosides, steroids, flavonoids, saponins, etc., the results were indicated in Table 1.

Physicochemical parameters of *E. scandens* seed flour and starch extracts

Physicochemical parameters revealed that the gelation temperature obtained was in the range of 118–129°C. The pH of 1% solution was in the range of 6.32–6.98. Viscosity was slightly higher than water and was in the range of 1.856–2.312 cps. Swelling index was in the range of 58–78%. Water absorption index is very high and microbial growth was nil in almost all starches. The results were indicated in Table 2.

Acute toxicity studies on albino mice

Acute toxicity studies on Albino Mice were conducted for extracted starches at different dose levels.

It was observed that all groups of mice were healthy with no physiological changes in their behavior up to the 1000 mg/kg dose. The mice were found to exhibit corner sitting and salivation in their physiological behavior at 2000 mg/kg body weight dose; however, no incidence of death occurred in any group of mice even at the higher dose levels. The results were indicated in Table 3.

Formulation of atorvastatin FDTs

Atorvastatin FDTs with various concentrations of ESS4 and CCS were prepared by wet granulation technique using isopropyl alcohol as the granulating fluid. Formulations F1–F5 were prepared by using 2.5–15% of alkali extracted starch (ESS4) starch. Formulations F7–F11 were prepared using 2.5–15% of CCS whereas the formulation F6 does not contain any superdisintegrant. The compositions were given in Table 4.

Table 9: Post-compression parameters of formulations F5 and F11 under accelerated stability conditions

Formulation	Storage condition	Hardness (kg/cm²)	Friability (% loss)	Dispersion test	Wetting time (s)	Drug content (mg/tablet)
F5	Before Storage	3.5±0.1	0.2	Passed	45	10.04±0.2
	25±2°C, 60±5% RH	3.4±0.2	0.3	Passed	45	9.95±0.2
	40±2°C, 75±5% RH	3.4±0.1	0.2	Passed	46	9.90±0.2
F11	Before Storage	3.5±0.1	0.2	Passed	61	10.02±0.6
	25±2°C, 60±5% RH	3.4±0.4	0.3	Passed	62	9.75±0.6
	40±2°C, 75±5% RH	3.4±0.2	0.3	Passed	65	9.25±0.6

Evaluation of pre-compression parameters

The pre-compression parameter values obtained for various prepared granules were given in Table 5. The angle of repose, Carr's index, and Hausner's ratio values obtained for various prepared granules were within the range specified. Thus, all the prepared granules were found to be stable and suitable for compression as FDTs.

Evaluation of post-compression characteristics of FDTs

The wet granulation process was found to be suitable for compressing prepared granules as FDTs. All the batches of tablets were compressed under identical conditions to minimize processing variables. Then, the compressed tablets were further evaluated for post-compression parameters such as weight uniformity, hardness, friability, wetting time, dispersion test, and drug content. The results were given in Table 6. Weight uniformity, hardness, and friability loss of all tablet formulations were within the specified limits. The wetting time values were in the range of 60–220 s. Drug content estimated for all the tablet formulations was highly uniform in the range 9.32 ± 0.4–10.79 ± 0.6 mg. Thus, all the batches of tablet formulations were found to be stable and suitable for further studies.

In vitro dissolution studies of atorvastatin FDTs

Dissolution studies were carried on all the FDT formulations using U.S.P paddle method (apparatus II) with phosphate buffer pH 6.8 as dissolution medium by maintain the bath temperature at 37 ± 1°C and while the paddles were operated at 50 rpm. The dissolution profiles of all the FDTs were given in Tables 7–8 and shown in Figures 1–2. The pure drug formulation, F6 without any superdisintegrant showed only 71.89% drug release in 60 min whereas the formulations F1–F5 containing 2.5–15% of ESS4 starch exhibited 78.35–98.65% of drug release. The formulations F7–F11 containing 2.5–15% of CCS exhibited 71.89–98.18% of drug release which is almost nearer to that of the ESS4 starch formulations. It was observed that as the type of starch as superdisintegrant and the proportion of superdisintegrant have greatly influenced the dissolution parameters of various formulations. The superdisintegrant ESS4 has exhibited comparative dissolution profile with that of standard superdisintegrant CCS. Formulation F5 containing 15% w/w ESS4 as superdisintegrant exhibited similar dissolution profile with that of formulation F11 prepared by 15% w/w CCS. Several studies have been conducted earlier indicating the effect of superdisintegrants over solubility enhancement.[12] They suggest the usage of a mixture of superdisintegrants rather than single.[13] Recent studies suggest the application of natural starches as superdisintegrants.[14,15] They also prove the equal efficacy of natural starches and already established superdisintegrants.

Characterization of atorvastatin FDTs

The FTIR spectral investigations were carried out on the pure drug of Atorvastatin, ESS4, CCS, and FDTs of Atorvastatin F5 and F11. Atorvastatin pure drug exhibited sharp peaks at 3133.67 cm^{-1}, 1409.78 cm^{-1}, 1223.10 cm^{-1}, 1155.96 cm^{-1}, 884.49 cm^{-1}, 842.85 cm^{-1}, 751.80 cm^{-1}, and 692.26 cm^{-1} indicating the presence of ≡C-H stretching, NO_2 stretching, ≡C-O- stretching, and CH bonds of aromatic rings. Starch extracted from *E. scandens*, ESS4 exhibited sharp peaks at 3049.42 cm^{-1}, 1744.80 cm^{-1}, 1645.74 cm^{-1}, 1242.69 cm^{-1}, and 1014.79 cm^{-1} indicating the presence of ≡C-H stretching, C=O stretching, C=C stretching, and ≡C-O- stretching. Whereas CCS exhibited sharp peaks at 3235.60 cm^{-1}, 2136.42 cm^{-1}, 1606.39 cm^{-1}, 900.17 cm^{-1}, and 736.24 cm^{-1} indicating the presence of ≡C-H stretching, -C≡C- stretching, C=C stretching, and CH bonds of aromatic rings. Formulation F5, FDTs made with Atorvastatin and ESS4 combination exhibited strong peaks at 3193.11 cm^{-1}, 1638.54 cm^{-1}, 1411.05 cm^{-1}, 1022.39 cm^{-1}, 895.45 cm^{-1}, and 708.41 cm^{-1} indicating the presence of ≡C-H stretching, C=C stretching, NO_2 stretching, ≡C-O- stretching, and CH bonds of aromatic rings. Formulation F11, FDTs made with Atorvastatin and CCS combination exhibited strong peaks at 3137.06 cm^{-1}, 1638.13 cm^{-1}, 1413.59 cm^{-1}, 1059.33 cm^{-1}, 894.94 cm^{-1}, and 669.34 cm^{-1} indicating the presence of ≡C-H stretching, C=C stretching, NO_2 stretching, ≡C-O- stretching, and CH bonds of aromatic rings. The detailed spectral elucidations were shown in Figure 3.

The DSC thermographic studies were carried out on the pure drug of Atorvastatin, ESS4, CCS, and FDTs of Atorvastatin F5 and F11. These studies exhibited broad endothermic peaks at 257.58°C, 266.73°C, and 350.3°C for Atorvastatin pure drug, a broad endothermic peak at 311.1°C for ESS4, a sharp exothermic peak at 319.1°° for CCS, a broad endothermic peak at 326.04°C, and a sharp exothermic peak at 377.39°C for F5 formulation, which is an FDT made with Atorvastatin and ESS4, indicating that there is a slight shift in temperature for drug and ESS4. A sharp endothermic peak at 270.12°C and a broad exothermic peak at 313.8°C for formulation F11, which is an FDT made with Atorvastatin and CCS was observed indicating that there is a slight shift in temperature for drug and CCS. The detailed thermographs were shown in Figure 4.

SEM images were taken for *E. scandens* seed powder, ESS4, pure drug of Atorvastatin, CCS, and a blend of Atorvastatin with ESS4 and a blend of Atorvastatin with CCS. It was observed that the starch grains in *E. scandens* seed powder were covered with some mucilage/resinous mass which was clearly represented in the image. The ESS4 starch exhibited free-flowing spherical low dense form of starch grains without any mucilage/resinous coverage. Atorvastatin pure drug exhibited crystalline form. CCS exhibited blunt tubular shaped crystals. The SEM image of Atorvastatin with ESS4 clearly exhibited uniform dispersion of drug with spherical,

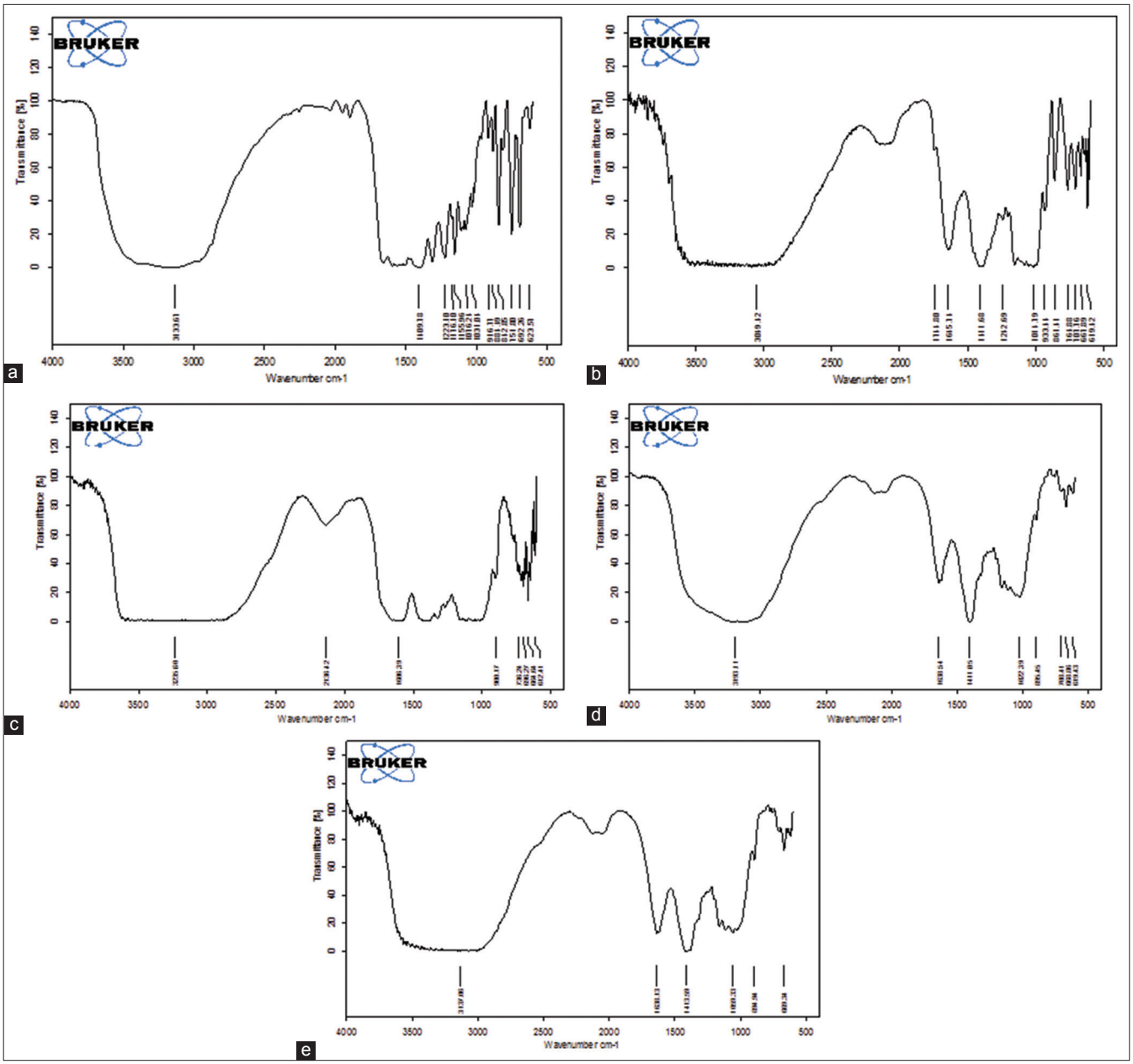

Figure 3: Fourier transform infrared spectra: (a) Atorvastatin (b) ESS4 (c) CCS (d) F5 (e) F11. ESS4: *Entada scandens* seed starch extracted by 0.5% sodium hydroxide; CCS: Croscarmellose sodium; F5: FDT of Atorvastatin+ESS4; F11: FDT of Atorvastatin+CCS

globular starch grains. The SEM image of Atorvastatin with CCS showed the uniform dispersion of drug with blunt tubular crystals of CCS. The detailed SEM images were shown in Figure 5.

XRD diffraction studies were carried out for a pure drug of Atorvastatin, ESS4, CCS, and FDTs of Atorvastatin F5 and F11. The X-ray diffractogram of Atorvastatin showed sharp and intense peaks at diffraction angles (2θ) of 22.930°, 28.334°, 38.518°, and 39.370° indicating a typical crystalline pattern. Whereas ESS4 showed intense peaks at diffraction angles (2θ) of 17.730°, 24.251°, and 33.531° indicating crystalline nature. CCS showed sharp and intense peaks at diffraction angles (2θ) of 21.770°, 22.741°, 25.292°, and 30.210° indicating crystalline nature. Formulation, F5 which is a FDT of Atorvastatin and ESS4 showed sharp and intense peaks at diffraction angles (2θ) of 21.550°, 25.530°, 31.250°, and 39.370° indicating the disappearance of some of the crystalline peaks of drug and ESS4 which suggest the formation of a new solid phase. Formulation, F11 which is an FDT of Atorvastatin and CCS showed sharp and intense peaks at diffraction angles (2θ) of 15.055° and 28.349° indicating the disappearance of most of the crystalline peaks of drug and CCS which suggest the formation of a new solid phase with a lower degree of crystallinity due to complexation. The detailed diffractograms were shown in Figure 6.

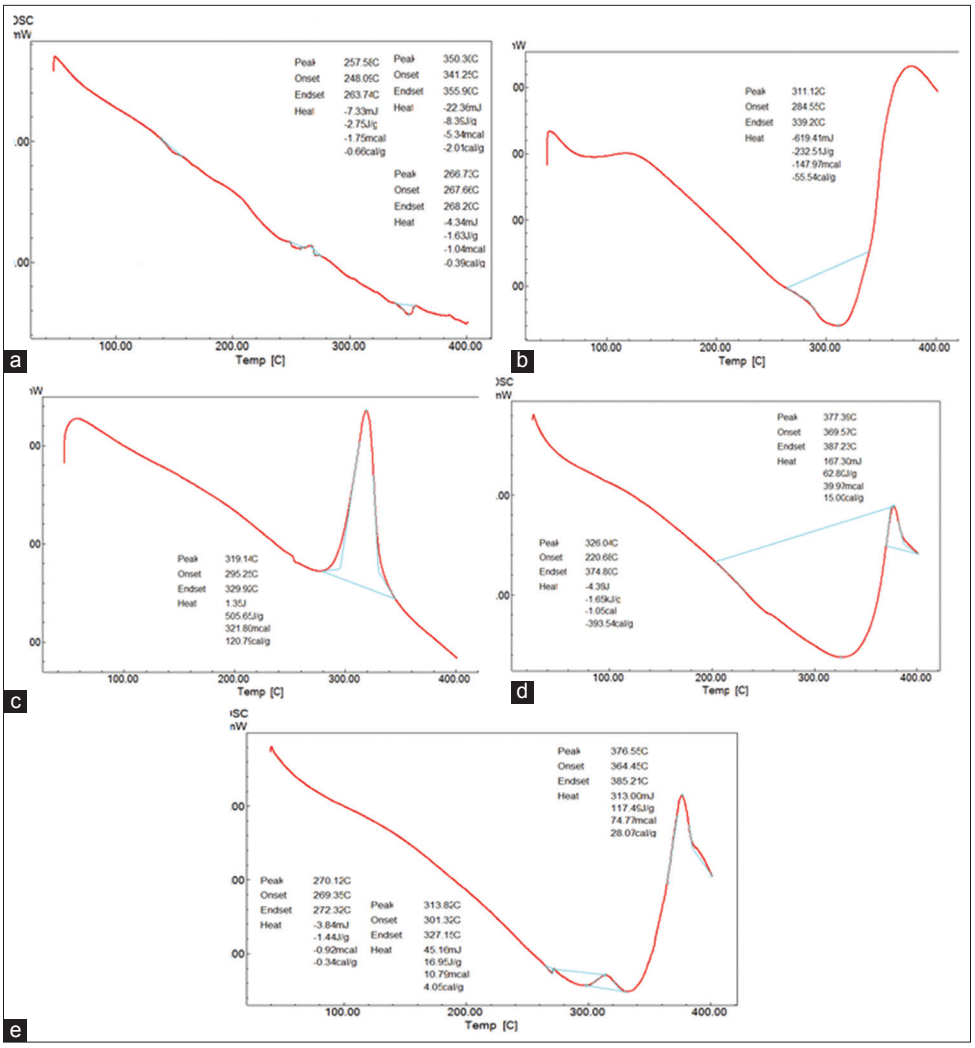

Figure 4: Differential scanning calorimetry thermograms: (a) Atorvastatin, (b) ESS4, (c) CCS, (d) F5, and (e) F11; ESS4: *Entada scandens* seed starch extracted by 0.5% sodium hydroxide; CCS: Croscarmellose sodium; F5: FDT of Atorvastatin+ESS4; F11: FDT of Atorvastatin+CCS

Accelerated stability studies of atorvastatin FDTs

The FDTs F5 and F11 containing Atorvastatin which showed good *in vitro* performance were subjected to accelerated stability studies. These studies were carried out by investigating the effect of temperature on the physical properties of the tablets and drug release from the FDTs. The results were indicated in Table 9.

The results, thus, indicated that there were no visible and physical changes observed in the FDTs after storage. Weight uniformity, hardness, friability, wetting time, dispersion test, and drug content were found to be uniform before and after storage at different conditions. It was also observed that there was no significant change in drug release from the FDTs. Thus, the drug release characteristics of FDTs designed were found to be quite stable.

CONCLUSION

The starches obtained from *E. scandens* seeds were crisp, slightly granular, and free-flowing powders and are stable in nature. The starch ESS4, extracted by 0.5% sodium hydroxide is found to be best and is used as superdisintegrant for preparation of FDTs. Acute toxicity studies on Albino Mice indicated the safety of the superdisintegrant. Atorvastatin FDTs were prepared using various concentrations of ESS4 and CCS and were subjected to *in vitro* dissolution studies. From these studies, it was observed that the proportion of starch as superdisintegrant has influenced the dissolution parameters of various formulations. Similar dissolution profiles were observed for formulations, F5 containing 15%w/w of ESS4, and F11 containing 15%w/w of CCS as superdisintegrants. The possible mechanism of superdisintegrant effect of these starches might be the rapid uptake of water, followed by swelling which causes the elevation of hydrostatic pressure in a tablet that leads to the faster disintegration of tablets.

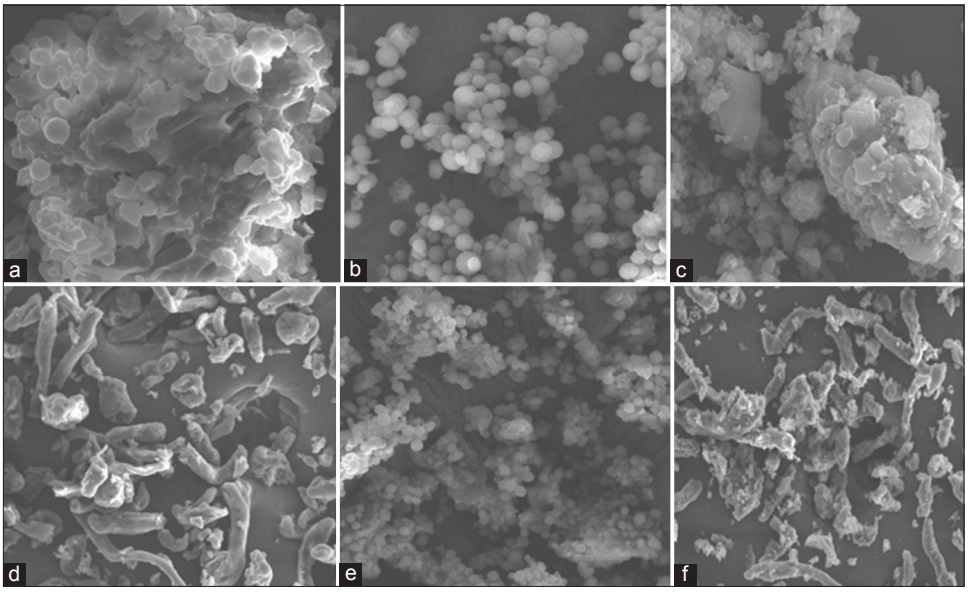

Figure 5: Scanning electron microscopy images: (a) *Entada scandens* raw seed powder (b) ESS4 (c) Atorvastatin (d) CCS (e) A blend of atorvastatin + ESS4 (f) A blend of Atorvastatin + CCS; ESS4: *Entada scandens* seed starch extracted by 0.5% sodium hydroxide; CCS: Croscarmellose sodium

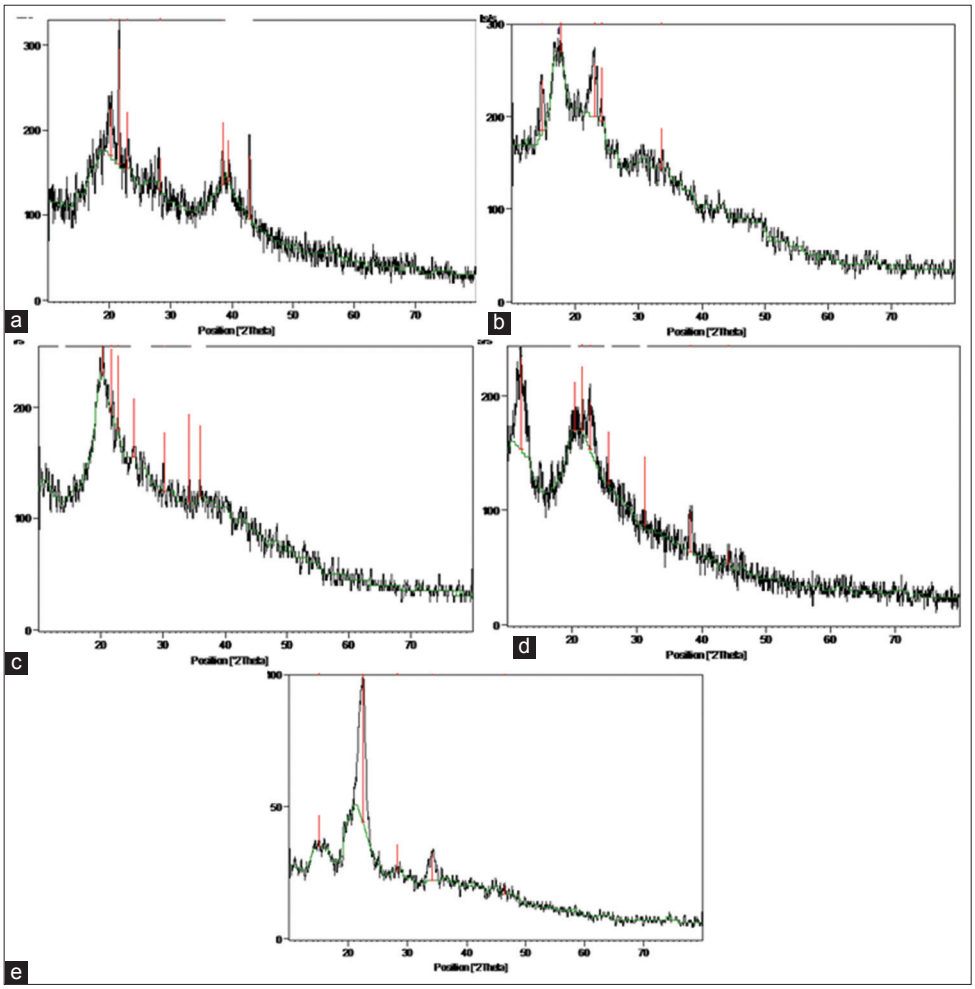

Figure 6: X-ray diffraction diffractograms: (a) Atorvastatin (b) ESS4 (c) CCS (d) F5 (e) F11; ESS4: *Entada scandens* seed starch extracted by 0.5% sodium hydroxide; CCS: Croscarmellose sodium; F5: FDT of atorvastatin+ESS4; F11: FDT of Atorvastatin+CCS

The optimized formulations were subjected to FTIR and DSC analysis to study the drug-excipient interactions, which revealed no such interactions. Similarly, XRD studies were conducted to know the crystalline and amorphous nature of the samples. The optimized formulations F5 and F11 were also subjected to accelerated stability studies, which revealed that there were no significant changes in physical parameters and drug content even after the stability studies at various storage conditions which indicate that these formulations were stable.

Based on the above studies, it may be concluded that the Atorvastatin FDTs prepared using 0.5% sodium hydroxide extracted ESS4 showed rapid drug release.

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REFERENCES

1. Sreenivas SA, Gadad AP, Patil MB. Formulation and evaluation of Ondansetron hydrochloride directly compressed mouth dissolving tablets. Indian Drugs 2006;43:35-7.
2. Thomus R. Fast dissolving tablets: An overview. Eur J Pharm Sci 2007;32:58-68.
3. Bhowmik D, Chiranjib B, Yadav J, Chandira RM, Sampath KP. Emerging trends of disintegrants used in formulation of solid dosage form. Schol Res Lib 2010;2:495-04.
4. Sunada H, Bi Y. Preparation, evaluation and optimization of rapidly disintegrating tablets. Powder Technol 2002;122:188-98.
5. Dey SK, Rahman M, Ahmed A, Khatun A, Siraj A. Phytochemical screening and pharmacological activities of *Entada scandens* seeds. Int J Appl Res Nat Prod 2013;6:34-9.
6. Furie KL. High dose statins should only be used in atherosclerotic strokes. Stroke 2012;43:1994-5.
7. Fateatun N, Jiaur RM, Sultan MM, Sorifa A, Aminul IT, Ahmed M. Physicochemical properties of flour and extraction of starch from jack fruit seed. Int J Nutr Food Sci 2014;3:347-54.
8. Menaka T, Nagaraja G, Yogesh DB, Sunil Kumar US, Prakash L. Physicochemical properties of flour and isolated starch from jackfruit seeds (*Artocarpus heterophyllus*). Res J Pharm Sci 2011;1:14-8.
9. Muhammad A. Acute toxicity of herbal drug somina in rats and mice. Pharmacol Pharm 2015;6:185-9.
10. Okunlola A, Odeku OA. Comparative evaluation of starches obtained from *Dioscorea* species as intragranular tablet disintegrants. J Drug Deliv Sci Technol 2008;18:445-7.
11. Shukla D, Subhashis C, Sanjay S, Brahmeshwar M. Mouth dissolving Tablets II: An overview of evaluation techniques. Pharm Sci 2009;77:327-41.
12. Biraju P, Dhaval P, Ramesh P, Chirag P, Tejas S, Sanja SD. Development and *in vitro* evaluation of fast dissolving tablets of glipizide. Int J Pharm Pharm Sci 2009;1:15-8.
13. Prasanna LA, Anand KM, Vamsi KM, Annie VK, Ashwini G. Formulation and development of irbesartan (poorly water soluble drug) immediate release tablets. Int Res J Pharm 2012;3:34-7.
14. Roy CP, Bhattacharyya AK, Chattopadhyay P. Study on functional properties of raw and blended jackfruit seed flour (a non-conventional source) for food application. Ind J Nat Prod Res 2012;3:56-9.
15. Vidyadhara S, Sasidhar RL, Lakshmi HD, Vijetha P, Vijetha K. Studies on jack fruit seed starch as a novel natural superdisintegrant for the design and evaluation of irbesartan fast dissolving tablets. Integr Med Res 2017;6:280-91.

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