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FORMULATION AND EVALUATION OF FEBUXOSTAT FAST DISSOLVING TABLETS USING *STERCULIA FOETIDA* SEED STARCH AS EXCIPIENT BY LYOPHILIZATION TECHNIQUE

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Keywords:

Sterculia foetida, Febuxostat, Fast dissolving tablets, Lyophilization, Croscarmellose sodium.

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ABSTRACT: The present work is focused on the formulation of Febuxostat fast dissolving tablets by lyophilization technique using natural starch extracted from *Sterculia foetida* seeds. Starches were extracted using the alkali method, *i.e.*, sodium hydroxide at 0.1%, 0.25%, and 0.5% concentrations and water from *Sterculia foetida* seed powder. These starches were evaluated for phytochemical and physicochemical tests. Tablets were prepared using Febuxostat, *Sterculia foetida* seed starch, and croscarmellose sodium in various concentrations using direct compression technique. Various pre and post-compression parameters were performed along with in vitro drug release studies, characterization studies like FTIR, DSC, SEM, XRD, and accelerated stability studies. Phytochemical tests revealed the presence of only starch in all the extracts. The starch prepared from 0.1% sodium hydroxide (SFS2) showed the best physicochemical properties. From in vitro dissolution studies, it was observed that formulations FS6 and FS12 containing 15% w/w of SFS2 and 15% w/w of croscarmellose sodium respectively showed faster disintegration and enhanced dissolution rate compared with other formulations. Febuxostat tablets were further prepared by lyophilization technique. The lyophilized product FSL5 containing 12.5% w/w of SFS2 showed more drug release when compared to FS6. Fourier Transform Infra-Red (FT-IR) spectroscopy and Differential Scanning Calorimetry (DSC) studies revealed that there were no major interactions between the drug and excipients. X-Ray Diffraction (XRD) studies revealed the nature of formulations. Thus the tablets prepared using *Sterculia foetida* seed starch by lyophilization technique revealed the super disintegrant property of starch.

INTRODUCTION: The oral route of drug administration is widely preferred due to its ease of intake. But in geriatrics and children, it is difficult to swallow the drug.

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In order to reduce such difficulties, fast-dissolving tablets (FDTs) are developed. These tablets, when contact with saliva in the mouth, rapidly disintegrate and releases drug [1]. Fast dissolving tablets are widely preferred due to their advantages like patient compliance, rapid action, increased bioavailability, and quick disintegration [2].

These are mostly prepared by wet granulation technique. Usage of certain superdisintegrants like sodium starch croscarmellose, polyvinyl pyrrolidine, poloxamer-188, starch glycolate, *etc*.

gives instant degradation property to tablets. Even at low concentrations, they are highly effective. They are mixed to the tablet to promote the breakup of tablets and capsules "slugs" into smaller fragments in an aqueous environment, which increases the available, total surface area of the tablet and promotes the rapid release of the drug. They also promote moisture penetration, which leads to disruption of tablet matrix [3]. Natural super-disintegrants are nowadays gaining more importance in the pharmaceutical field due to their easy availability, cheaper in cost, non-irritating, and non-toxic nature. Several plant-derived gums and mucilages have superdisintegrant property. Extensive research work is being carried out on such substances which enhance the water solubility of BCS Class-II drugs with low solubility and high permeability properties. Recent studies revealed the applications of plant components from Isapgula, gum karaya, fenugreek seed mucilage, guar gum,z etc. as superdisintegrants in formulating fast dissolving tablets (FDTs) [4].

Lyophilization, also called as freeze-drying is a method of tablet preparation that has many advantages like physical resistance, hygroscopicity, and a low dose of drug incorporation. Due to their high porosity, lyophilized tablets undergo faster disintegration in the oral cavity than other formulations [5]. In the present study, an attempt was made to extract starch from *Sterculia foetida* seeds and to use it as superdisintegrant for formulating fast dissolving tablets using lyophilization technique. *Sterculia foetida,* which belongs to the family Malvaceae, grows in India, Taiwan, Indonesia, and the Philippines. The fruit consists of 4 to 5 follicles, each containing 10-15 seeds. The seeds are covered with a tough, parchment-like skin. These are rich in starch contents [6]. Febuxostat which is an anti-urolithiasis agent is selected as a drug candidate for the present study. It mainly acts by non-competitively inhibiting the enzyme xanthine oxidase. This prevents the conversion of hypoxanthine and xanthine to uric acid, thereby preventing the formation of crystals in kidneys. The bioavailability of Febuxostat is approximately 49%. More than 99% of the drug is bound to plasma proteins. It has an approximate elimination half-life of 5-8 h [7]. Based on pharmacokinetic and pharmacodynamic parameters, Febuxostat is selected as a drug of choice for the present study.

MATERIALS AND METHODS:

Materials: Febuxostat was a gift sample from Mylan Laboratories Ltd. (Hyderabad, India). Croscarmellose sodium was a gift sample from NATCO Pharma Ltd. (Hyderabad, India). Sodium hydroxide, sucrose, magnesium stearate, and talc were procured from S.D Fine Chem. Ltd. (Mumbai, India). *Sterculia foetida* seeds were procured from the local market (Tirupathi, Andhra Pradesh, India).

Extraction of Starch from *Sterculia Foetida* Seeds: *Sterculia foetida* seed starch was isolated using aqueous and alkali extraction techniques [8]. 5 g *Sterculia foetida* 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 the remaining sediment was washed with distilled water three times. The filtrates were combined and precipitated overnight at 40 ºC. The supernatant was discarded, and the crude starch was cleaned with distilled water. This step was repeated three times, and the starch cake was dried at 40 ºC for 24 h in the 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 *Sterculia Foetida* Seed Powder and Extracted Starches: The raw *Sterculia foetida* seed powder and starches extracted were subjected to various phytochemical tests for identification of carbohydrates, proteins, alkaloids, glycosides, steroids, flavonoids and saponins [9]. The results were indicated in **Table 1**.

Evaluation of Physicochemical Properties of *Sterculia Foetida* Seed Powder and Extracted Starches: Various physicochemical properties like gelatinization temperature, pH, viscosity, swelling index, and water absorption index was evaluated using suitable methods [10]. All the results were indicated in **Table 2**.

Total Microbial Load of Isolated *Sterculia Foetida* Seed 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 agar medium was prepared and placed in an autoclave for 1 h. To this, bacterial culture like Escherichia coli was added, mixed well, and poured into petri plates and allowed to solidify for 10 min. After solidification, the starch powder was sprinkled and kept in an incubator for 24 h.

According to many pharmacopeias, in the case of excipients from natural origin, the total aerobic count should not be more than 1000 cfu/g, and total fungal count should not exceed 100 cfu/g.

Acidity: One gram of starch was added to 100 ml of ethanol (70 percent), which was previously neutralized to phenolphthalein solution. This solution was shaken for 1 h, filtered, and 50 ml of the filtrate was titrated with 0.1 M sodium hydroxide.

Fluorescence: 500 mg of starch powder was dissolved in an organic solvent and placed on a glass slide. The slide was examined under a UV cabinet for the presence of any fluorescent material.

Oxidizing Substances: To 5.0 g of sample, 10 ml of water and 1 ml of acetic acid were added and stirred until a homogeneous suspension was obtained. 0.5 ml of a freshly prepared saturated solution of potassium iodide was added, mixed and allowed to stand for 5 min.

Sulphated Ash: 1-2 g of the starch was placed in an accurately weighed crucible and ignited until thoroughly charred. Then it is cooled, and the residue was moistened with 1 ml of sulphuric acid. It was heated gently until white fumes are no longer evolved and ignited at 800 ºC until black particles have disappeared.

The crucible was cooled and few drops of sulphuric acid were added and heated. Then it was weighed. This procedure was repeated until two successive weighing doesn't differ by more than 0.5 mg.

Loss on Drying: Loss on drying is widely used to determine the moisture content of a sample, although occasionally it may refer to the loss of any volatile matter from the sample. Not more than 15% (for all starches except potato starch) and not more than 20% (for potato starch) of weight loss should be obtained. It was determined by drying 0.2 g of starch in an oven at 105 ºC.

Test for Amylose Content: 100 mg of isolated starch sample was taken, and to it, 1ml of ethanol and 9 ml of 1 N sodium hydroxide were added and kept aside for overnight. The suspension was thoroughly mixed. The dispersed sample was transferred to a 100 ml volumetric flask and diluted to the mark with distilled water. 5 ml of test starch solution was pipetted into a 100 ml volumetric flask, and 1 ml of 1 N glacial acetic acid, 2 ml of Iodine solution (0.02 N) were added. The volume was made up to 100 ml with distilled water, and the absorbance was measured at 620 nm.

Formulation of Febuxostat Tablets: Febuxostat tablets were prepared by direct compression technique. The drug concentration was maintained constant, while the concentration of *Sterculia foetida* seed starch was increased. The raw materials were individually weighed and were then converted into damp mass by 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. The compositions of various tablet formulations were given in **Table 3**. 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 the angle of repose, Carr's index, and Hausner's ratio [11]. The results were given in **Table 4**.

Evaluation of Post Compression Parameters: The compressed tablets were further evaluated for post-compression parameters such as weight uniformity, hardness, friability, wetting time, dispersion test, and drug content [12]. The results were given in **Table 5**.

***In-vitro* Dissolution Studies of Febuxostat Tablets:** Dissolution studies for each tablet formulation were performed in a calibrated 8 station dissolution test apparatus (LAB INDIA

DS8000) equipped with paddles (USP apparatus II method) employing 900 ml of 0.05 M phosphate buffer pH 6.0 as a dissolution medium [13]. The paddles were operated at 50 rpm, and temperature was maintained at 37 ± 1 ºC throughout the experiment. The samples were withdrawn at 5, 10, 15, 20 and 30 min and replaced with an equal volume of same dissolution medium to maintain the constant volume throughout the experiment. Samples withdrawn at various time intervals were suitably diluted with the same dissolution medium, and the amount of the drug dissolved was estimated by Lab India double beam U.V spectrophotometer (UV 3000+) at 315 nm. The dissolution studies on each formulation were conducted in triplicate. The dissolution profiles for all formulations were given in **Tables 6**, **7,** and **Fig. 1**, **2**.

Preparation and Evaluation of Febuxostat Tablets by Lyophilization Technique: Febuxostat granules were prepared similar to that of tablet formulation and were subjected to lyophilization [14]. Then the granules were taken out and half of the quantity of *Sterculia foetida* seed starch was added to lyophilized lactose granules and blended for 15 min using double cone blender. Flavoring agent was added to powdered mass and blended with 1% talc, magnesium stearate, and compressed as tablets using CLIT 10 station mini-press. Various pre and post-compression parameters were also evaluated for the prepared lyophilized Febuxostat granules. The results were indicated in **Tables 8** and **9**. The dissolution profiles for all formulations were given in **Tables 10**, **11,** and **Fig. 3**, **4**.

Characterization Studies: Based on dissolution studies, the optimized formulations were selected and subjected to Fourier transfer infrared (FTIR), and differential scanning calorimetry (DSC) studies to observe the drug-polymer interactions. X-Ray Diffraction (XRD) studies were conducted to detect the nature of formulations. Scanning electron microscopy (SEM) analysis was carried out to know surface characteristics. The results were shown in **Fig. 5**, **6**, **7** and **8**.

Statistical Analysis: The results obtained were statistically evaluated. As the procedures performed and the results obtained were in triplicates, the mean along with their standard error of mean (S.E.M) were calculated for weight uniformity, hardness, drug content and cumulative percentage drug release.

RESULTS AND DISCUSSION:

Extraction of Starch from *Sterculia Foetida* Seeds: The starches extracted from *Sterculia foetida* seeds were crisp, slightly granular, free-flowing and stable in nature.

TABLE 1: PHYTOCHEMICAL TESTS FOR *STERCULIA FOETIDA* SEED POWDER AND EXTRACTED STARCHES

Test	SFSP	SFS1	SFS2	SFS3	SFS4
Carbohydrates	+	+	+	+	+
Polysaccharides	+	+	+	+	+
Proteins	–	–	–	–	–
Alkaloids	+	–	–	–	–
Glycosides	–	–	–	–	–
Steroids	+	–	–	–	–
Flavonoids	+	–	–	–	–
Saponins	+	–	–	–	–

TABLE 2: EVALUATION OF PHYSICOCHEMICAL PROPERTIES OF *STERCULIA FOETIDA* SEED POWDER AND EXTRACTED STARCHES

Parameters	SFSP	SFS1	SFS2	SFS3	SFS4
Gelatinization temperature	194-200 °C	221-230 °C	232-240 °C	275-283 °C	225-232 °C
pH	6.40	7.01	7.21	7.79	7.98
Viscosity	1.672 cps	2.422 cps	2.029 cps	2.134 cps	2.024 cps
Swelling index	39	56	79	62	55
Water absorption index	186	262	294	255	240
Microbial growth	Absent	Absent	Absent	Absent	Absent
Loss on drying (%)	3.6	3.3	2.4	6.2	4.4
Oxidizing substances	No brown (or) blue color was observed	No brown (or) blue color was observed	No brown (or) blue color was observed	No brown (or) blue color was observed	No brown (or) blue color was observed
Fluorescence	No fluorescence observed	No fluorescence observed	No fluorescence observed	No fluorescence observed	No fluorescence observed
Acidity	Non acidified	Non acidified	Non acidified	Non acidified	Non acidified
Sulphated ash	0.09%	0.08%	0.06 %	0.04%	0.1%
Amylose content	5.49	4.59	18.70	13.98	11.14

Phytochemical Screening of *Sterculia foetida* Seed Flour and Starch Extracts: The raw *Sterculia foetida* seed powder (SFSP), starch extracted from water (SFS1) and 0.1% (SFS2),

0.25% (SFS3) and 0.5% (SFS4) sodium hydroxide were screened for the presence of various phytochemical constituents.

Evaluation of Physicochemical Properties of *Sterculia foetida* Seed Powder and Extracted Starches: All the parameters evaluated for *Sterculia foetida* seed powder and extracted starches were within specified Indian Pharmacopoeial limits. Of all the starches, SFS2 with high swelling and water absorption index was selected for the preparation of tablets.

Formulation of Febuxostat Tablets: Febuxostat tablets with various concentrations of *Sterculia foetida* seed starch (SFS2) and croscarmellose sodium (CCS) were prepared by direct compression technique. Formulations FS1 to FS6 were prepared by using 2.5 to 15% of SFS2 starch. Formulations FS7 to FS12 were prepared using 2.5 to 15% of CCS. Formulation FP doesn't contain any superdisintegrant. The composition of Febuxostat tablets was given in **Table 3**.

TABLE 3: COMPOSITION OF FEBUXOSTAT TABLETS WITH DIFFERENT POLYMER CONCENTRATIONS

Ingredient (mg/tablet)	Formulations												
	FP	FS1	FS2	FS3	FS4	FS5	FS6	FS7	FS8	FS9	FS10	FS11	FS12
Febuxostat	40	40	40	40	40	40	40	40	40	40	40	40	40
Lactose	202.5	196.25	190.0	183.75	177.50	171.25	165.0	196.25	190.0	183.75	177.50	171.25	165.0
SFS2	-----	6.25	12.50	18.75	25.0	31.25	37.5	-----	-----	-----	----	-----	-----
CCS	-----	-----	-----	-----	----	-----	-----	6.25	12.50	18.75	25.0	31.25	37.5
Saccharin Sodium	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Lemon Flavour	Q.S	Q.S	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	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	1.25	1.25
Total Weight	250	250	250	250	250	250	250	250	250	250	250	250	250

Evaluation of Pre-Compression Parameters: The pre-compression parameter values obtained for various prepared granules were given in **Table 4**. 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 fast-dissolving tablets.

TABLE 4: PRE - COMPRESSION PARAMETERS OF FEBUXOSTAT GRANULES

Formulation	Angle of Repose (^{0})	Carr's Index (%)	Hausner's Ratio
FP	33	22	1.23
FS1	28	19	1.21
FS2	25	16	1.18
FS3	24	14	1.16
FS4	23	13	1.15
FS5	22	13	1.15
FS6	21	12	1.13
FS7	27	20	1.19
FS8	26	18	1.18
FS9	25	17	1.17
FS10	24	15	1.16
FS11	23	15	1.14
FS12	22	13	1.13

Evaluation of Post Compression Parameters of Febuxostat Tablet Formulations: All the batches of tablets were compressed under identical conditions to minimize processing variables. They 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 5**. Weight uniformity, hardness, and friability loss of all tablet formulations were within the specified limits. All tablet formulations were found to be stable and suitable for further studies.

***In-vitro* Dissolution Studies of Febuxostat Tablets:** Dissolution studies were carried on Febuxostat tablets using the U.S.P paddle method (apparatus II) with 0.05 M phosphate buffer pH 6.0 as dissolution medium by maintaining the bath temperature at 37 ± 1 ºC and the paddles were operated at 50 rpm. The dissolution profiles of tablets were given in **Table 6-7** and shown in **Fig. 1-2**. Pure drug formulation, FP showed very less drug release. It was observed that the proportion of starch as superdisintegrant has greatly influenced the dissolution parameters of various formulations.

Formulation FS6 containing 15% w/w of SFS2 as superdisintegrant exhibited closer dissolution profile with that of formulation FS12 prepared by 15% w/w of CCS. Several studies have been carried out previously indicating the advantages of superdisintegrants in solubility enhancement [15]. Recent works focused on the natural starches application as superdisintegrants [16, 17]. They have successfully proved the efficacy of natural starches as pharmaceutical excipients.

TABLE 5: POST COMPRESSION PARAMETERS OF VARIOUS FEBUXOSTAT TABLET FORMULATIONS

Formulation	Weight uniformity (mg)	Hardness (kg/cm^2)	Friability (% loss)	Wetting Time (sec)	Dispersion time (sec)	Drug Content (mg/tablet)
FP	248 ± 1.41	3.4 ± 1.08	0.3	252	Passed	39.41 ± 1.22
FS1	249 ± 1.08	3.3 ± 1.11	0.4	174	Passed	38.27 ± 1.49
FS2	249 ± 1.67	3.2 ± 1.79	0.2	132	Passed	39.07 ± 1.75
FS3	250 ± 1.53	3.3 ± 1.63	0.2	108	Passed	38.61 ± 2.02
FS4	249 ± 1.46	3.3 ± 1.41	0.3	86	Passed	39.44 ± 1.58
FS5	250 ± 1.77	3.2 ± 1.88	0.2	72	Passed	40.04 ± 1.07
FS6	250 ± 1.20	3.2 ± 0.74	0.2	60	Passed	39.17 ± 1.27
FS7	248 ± 1.97	3.4 ± 1.14	0.4	185	Passed	39.47 ± 1.44
FS8	249 ± 1.84	3.2 ± 1.77	0.2	140	Passed	38.15 ± 1.68
FS9	249 ± 1.46	3.3 ± 1.40	0.3	118	Passed	39.02 ± 1.57
FS10	249 ± 1.13	3.2 ± 1.61	0.2	92	Passed	39.77 ± 1.41
FS11	250 ± 1.07	3.3 ± 1.24	0.3	80	Passed	40.21 ± 1.03
FS12	249 ± 1.66	3.2 ± 1.65	0.2	66	Passed	40.01 ± 1.73

TABLE 6: DISSOLUTION PROFILES OF FEBUXOSTAT TABLETS PREPARED BY DIRECT COMPRESSION METHOD (FS1 – FS6)

Time (min)	Cumulative % Drug Released (Mean ± S.E.M)						
	FP	FS1	FS2	FS3	FS4	FS5	FS6
5	12.78 ± 1.10	28.71 ± 1.38	32.69 ± 1.14	37.23 ± 1.05	42.45 ± 1.63	44.07 ±1.09	53.82 ± 1.42
10	18.07 ± 1.88	39.36 ± 1.84	45.69 ± 1.45	49.12 ± 1.43	64.07 ± 1.25	69.87 ± 1.92	78.49 ± 1.98
15	23.77 ± 1.71	49.80 ± 1.55	54.80 ± 1.19	57.41 ± 1.18	72.09 ± 1.37	75.45 ± 1.53	82.67 ± 1.29
20	28.80 ± 1.69	56.32 ± 1.17	62.11 ± 1.36	68.86 ± 1.96	75.87 ± 1.75	81.62 ± 1.64	87.56 ± 1.16
30	32.07 ± 1.34	61.69 ± 1.61	65.55 ± 1.60	69.07 ± 2.02	82.07 ± 1.10	84.84 ± 1.39	89.11 ± 1.07

TABLE 7: DISSOLUTION PROFILES OF FEBUXOSTAT TABLETS PREPARED BY DIRECT COMPRESSION METHOD (FS7 – FS12)

Time (min)	Cumulative % Drug Released (Mean ± S.E.M)						
	FP	FS7	FS8	FS9	FS10	FS11	FS12
5	12.78 ± 1.10	24.41 ± 1.20	29.49 ± 1.74	34.51 ± 1.47	40.41 ± 1.57	42.67 ± 1.56	49.79 ± 1.63
10	18.07 ± 1.88	33.17 ± 1.97	40.23 ± 1.12	45.81 ± 1.33	52.61 ± 1.31	64.32 ± 1.60	70.51 ± 1.05
15	23.77 ± 1.71	46.46 ±1.50	51.66 ± 1.51	54.37 ± 1.69	65.22 ± 1.47	70.72 ± 1.98	78.63 ± 1.33
20	28.80 ± 1.69	52.82 ± 1.33	59.31 ± 1.65	61.67 ± 1.28	71.52 ± 1.49	78.30 ± 1.40	83.21 ± 1.67
30	32.07 ± 1.34	59.54 ± 1.82	62.49 ± 1.87	65.63 ± 1.09	77.14 ± 1.69	81.55 ± 1.19	85.07 ± 1.27

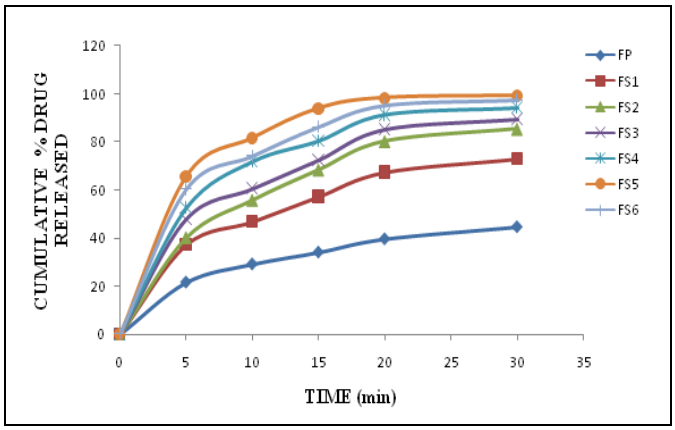

FIG. 1: DRUG RELEASE PROFILES OF FEBUXOSTAT TABLETS PREPARED BY DIRECT COMPRESSION METHOD (FS1 – FS6)

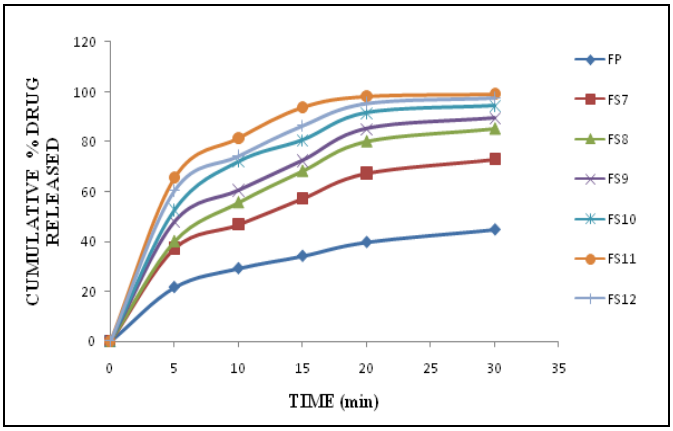

FIG. 2: DRUG RELEASE PROFILES OF FEBUXOSTAT TABLETS PREPARED BY DIRECT COMPRESSION METHOD (FS7 – FS12)

Formulation and Evaluation of Lyophilized Febuxostat Tablets: Febuxostat tablets were prepared by lyophilization technique with similar composition as given in **Table 3** by using water as a lyophilizing medium. The formulations were named as FLP to FSL12. Formulations FSL1 to FSL6 were prepared by using 2.5 to 15% of SFS2 starch. Formulations FSL7 to FSL12 were prepared using 2.5 to 15% of CCS.

Formulation FLP doesn't contain any super-disintegrant. The pre and post-compression parameter values obtained for various prepared granules were given in **Tables 8** and **9**. The values obtained were within the range specified and better when compared to tablet granules prepared before lyophilization. Thus, all the lyophilized granules were found to be stable and suitable for compression as fast-dissolving tablets.

TABLE 8: PRE - COMPRESSION PARAMETERS OF LYOPHILIZED FEBUXOSTAT GRANULES

Formulation	Angle of Repose (°)	Carr's Index (%)	Hausner's Ratio
FLP	30	21	1.21
FSL1	27	18	1.20
FSL2	24	15	1.17
FSL3	22	13	1.15
FSL4	21	12	1.14
FSL5	20	12	1.13
FSL6	22	14	1.15
FSL7	28	19	1.20
FSL8	25	17	1.17
FSL9	24	15	1.16
FSL10	22	14	1.15
FSL11	21	13	1.13
FSL12	22	14	1.14

TABLE 9: POST COMPRESSION PARAMETERS OF VARIOUS LYOPHILIZED FEBUXOSTAT TABLET FORMULATIONS

Formulation	Weight uniformity (mg)	Hardness (kg/cm^2)	Friability (% loss)	Wetting Time (sec)	Dispersion time (sec)	Drug Content (mg/tablet)
FLP	249 ± 1.57	3.4 ± 1.12	0.3	164	Passed	38.97 ± 1.82
FSL1	250 ± 1.77	3.2 ± 1.47	0.3	103	Passed	39.41 ± 1.67
FSL2	249 ± 1.31	3.3 ± 1.61	0.3	88	Passed	38.21 ± 1.70
FSL3	250 ± 1.44	3.3 ± 1.09	0.2	72	Passed	40.81 ± 1.95
FSL4	250 ± 1.10	3.2 ± 1.85	0.3	61	Passed	39.91 ± 1.12
FSL5	250 ±1.81	3.2 ± 1.62	0.2	44	Passed	40.01 ± 1.87
FSL6	249 ± 1.07	3.3 ± 1.57	0.2	56	Passed	39.55 ± 1.60
FSL7	249 ± 1.64	3.4 ± 1.87	0.4	124	Passed	38.52 ± 1.17
FSL8	250 ±1.71	3.3 ± 1.91	0.3	96	Passed	39.31 ± 1.53
FSL9	249 ± 1.63	3.2 ± 1.01	0.3	80	Passed	40.14 ± 1.21
FSL10	249 ±1.47	3.2 ± 1.65	0.2	71	Passed	39.90 ± 1.22
FSL11	250 ± 1.91	3.3 ± 1.80	0.3	53	Passed	40.11 ± 1.72
FSL12	249 ± 1.28	3.4 ± 1.33	0.2	65	Passed	39.35 ± 1.40

***In-vitro* Dissolution Studies of Lyophilized Febuxostat Tablet Formulations:** Dissolution studies were carried on lyophilized Febuxostat tablet formulations using U.S.P paddle method (apparatus II) with 0.05 M phosphate buffer pH 6.0 as dissolution medium by maintaining the bath temperature at 37 ± 1 ºC and the paddles were operated at 50 rpm. The dissolution profiles of tablets were given in **Table 10-11** and shown in **Fig. 3-4**. Pure drug formulation, FP showed very less drug release. It was observed that the proportion of starch as superdisintegrant has greatly influenced the dissolution parameters of various formulations. Formulation FSL5 containing 12.5% w/w of SFS2 as superdisintegrant exhibited a more dissolution profile than that of FS6. Past studies have proved the efficiency of the Lyophilization technique along with the usage of natural polymers in solubility enhancement of poorly soluble drugs [18].

TABLE 10: DISSOLUTION PROFILES OF FEBUXOSTAT TABLETS PREPARED BY LYOPHILIZATION TECHNIQUE (FSL1 – FSL6)

Time (min)	Cumulative % Drug Released (Mean ± S.E.M)						
	FLP	FSL1	FSL2	FSL3	FSL4	FSL5	FSL6
5	24.64 ±1.79	39.18 ± 1.93	44.16 ± 1.15	48.95 ± 1.74	56.64 ± 1.19	65.67 ± 1.34	60.36 ± 1.41
10	32.20 ± 1.35	48.72 ± 1.09	58.76 ± 1.21	63.50 ± 1.29	79.00 ± 1.26	88.61 ±1.76	74.17 ± 1.37
15	38.14 ± 1.20	57.14 ± 1.64	69.39 ± 1.99	76.44 ± 1.82	88.64 ± 1.22	94.94 ± 1.81	86.28 ± 1.43
20	45.67 ± 1.19	69.21 ± 1.88	82.26 ± 1.31	86.14 ± 1.04	93.54 ± 1.34	98.28 ± 1.59	92.19 ± 1.96
30	49.71 ± 1.46	75.77 ± 1.54	86.37 ± 1.35	90.35 ± 1.28	95.35 ± 1.89	99.16 ± 1.25	96.40 ± 1.07

TABLE 11: DISSOLUTION PROFILES OF FEBUXOSTAT TABLETS PREPARED BY LYOPHILIZATION TECHNIQUE (FSL7 – FSL12)

Time (min)	Cumulative % Drug Released (Mean ± S.E.M)						
	FLP	FSL7	FSL8	FSL9	FSL10	FSL11	FSL12
5	24.64 ± 1.79	35.11 ± 1.51	40.44 ± 1.30	43.22 ± 1.49	51.97 ± 1.32	61.67 ± 1.20	57.78 ± 1.63
10	32.20 ± 1.35	44.64 ± 1.29	55.10 ± 1.47	57.63 ± 1.74	73.73 ± 1.55	84.21 ± 1.82	70.24 ± 1.90
15	38.14 ± 1.20	52.23 ± 1.78	64.22 ± 2.04	72.81 ± 1.60	82.61 ± 1.89	92.41 ± 1.09	84.53 ± 1.61
20	45.67 ± 1.19	63.21 ± 1.76	78.99 ± 1.71	83.08 ± 1.18	89.11 ± 1.40	95.51 ± 1.22	90.20 ± 1.08
30	49.71 ± 1.46	70.15 ± 1.77	82.53 ± 1.14	86.30 ± 1.45	93.31 ± 1.75	97.50 ± 1.16	94.51 ± 2.11

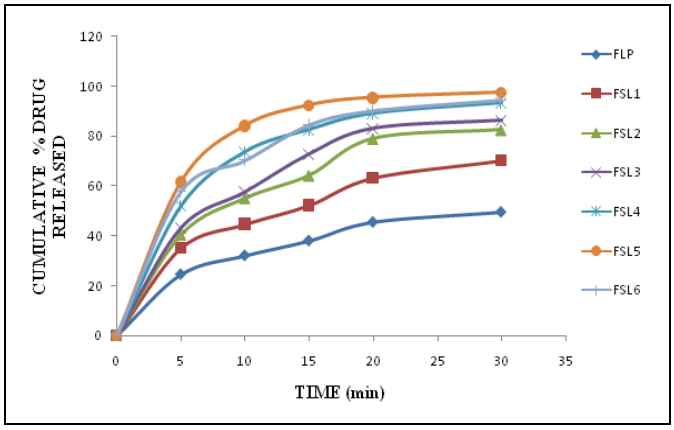

FIG. 3: DRUG RELEASE PROFILES OF FEBUXOSTAT TABLETS PREPARED BY LYOPHILIZATION TECHNIQUE (FSL1 – FSL6)

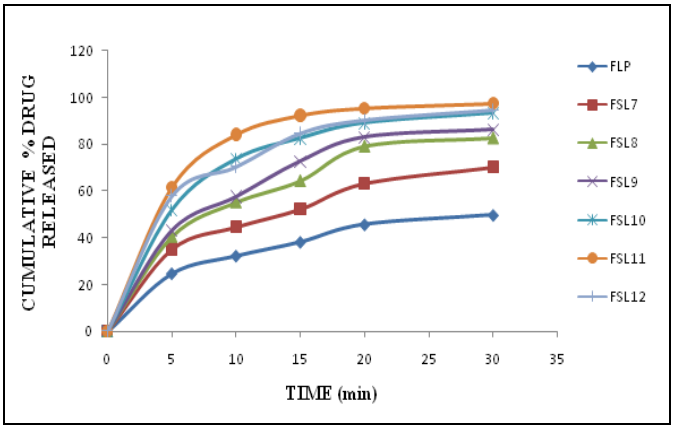

FIG. 4: DRUG RELEASE PROFILES OF FEBUXOSTAT TABLETS PREPARED BY LYOPHILIZATION TECHNIQUE (FSL7 – FSL12)

Comparative Dissolution Profiles of FDTs and Lyophilized Febuxostat Formulations: The lyophilized formulations of Febuxostat showed enhanced drug release when compared to that of Febuxostat fast dissolved formulations (FS1 - FS12). Further, the lyophilization technique has also reduced the amount of *Sterculia foetida* seed starch to be used in the formulation of Febuxostat tablets from 15% to 12.5% w/w. This was clearly indicated in the dissolution studies. This might be due to an increase in crystallinity, hygroscopicity, and porosity of lyophilized formulations.

Characterization Studies:

FT-IR Spectra: The FT-IR spectral investigations were carried out on Febuxostat pure drug, SFS2, CCS, fast-dissolving formulations of Febuxostat FS6, FS12 and lyophilized fast dissolving formulation FSL5. Febuxostat pure drug exhibited sharp peaks at 2228.03 cm^{-1}, 1617.88 cm^{-1}, 1510.30 cm^{-1}, 1283.08 cm^{-1}, 1044.84 cm^{-1}, 826.55 cm^{-1} and 767.05 cm^{-1} indicating the presence of C=C stretching, C=N stretching, N-O stretching, C=O stretching and –N=H wag. Starch extracted from *Sterculia foetida*, SFS2 exhibited sharp peaks at 3239.44 cm^{-1}, 2056.61 cm^{-1}, 1022.56 $cm^{-1,}$ and 862.41 cm^{-1} indicating the presence of C-H stretching, C=C stretching, ≡C-O- stretching and C-H bending. Whereas CCS exhibited sharp peaks at 1409.53 cm^{-1}, 1059.82 $cm^{-1,}$ and 897.37 $cm^{-1,}$ indicating the presence of C-H bending, C–N stretching, and O-H bending. Formulation FS6, made with Febuxostat and 15%w/w of SFS2 exhibited strong peaks at 3276.76 cm^{-1}, 2227.82 cm^{-1}, 2055.42 cm^{-1}, 1511.02 cm^{-1}, 1283.98 cm^{-1}, 1033.33 cm^{-1}, 875.46 $cm^{-1,}$ and 769.70 cm^{-1} indicating the presence of C-H stretching, C=C stretching, N-O stretching, C=O stretching, C-H bending and N-H wag.

Formulation FS12, made with Febuxostat and 15%w/w of CCS, exhibited strong peaks at 1638.13 cm^{-1}, 1413.59 cm^{-1}, 1059.33 $cm^{-1,}$ and 894.94 cm^{-1} indicating the presence of C=N stretching, -C≡N bending, C=N stretching and O-H bending. FSL5, a lyophilized FDT prepared with Febuxostat and 12.5% w/w of SFS2 exhibited peaks at 2228.05 cm^{-1}, 2058.57 cm^{-1}, 1510.12, 1283.88 cm^{-1}, 1033.18 cm^{-1}, 875.43 cm^{-1} and 753.22 cm^{-1} indicating presence of C=C stretching, C=O stretching, N-O stretching, C=O stretching, C-H bending and N-H wag. The detailed spectral elucidations were shown in **Fig. 5**.

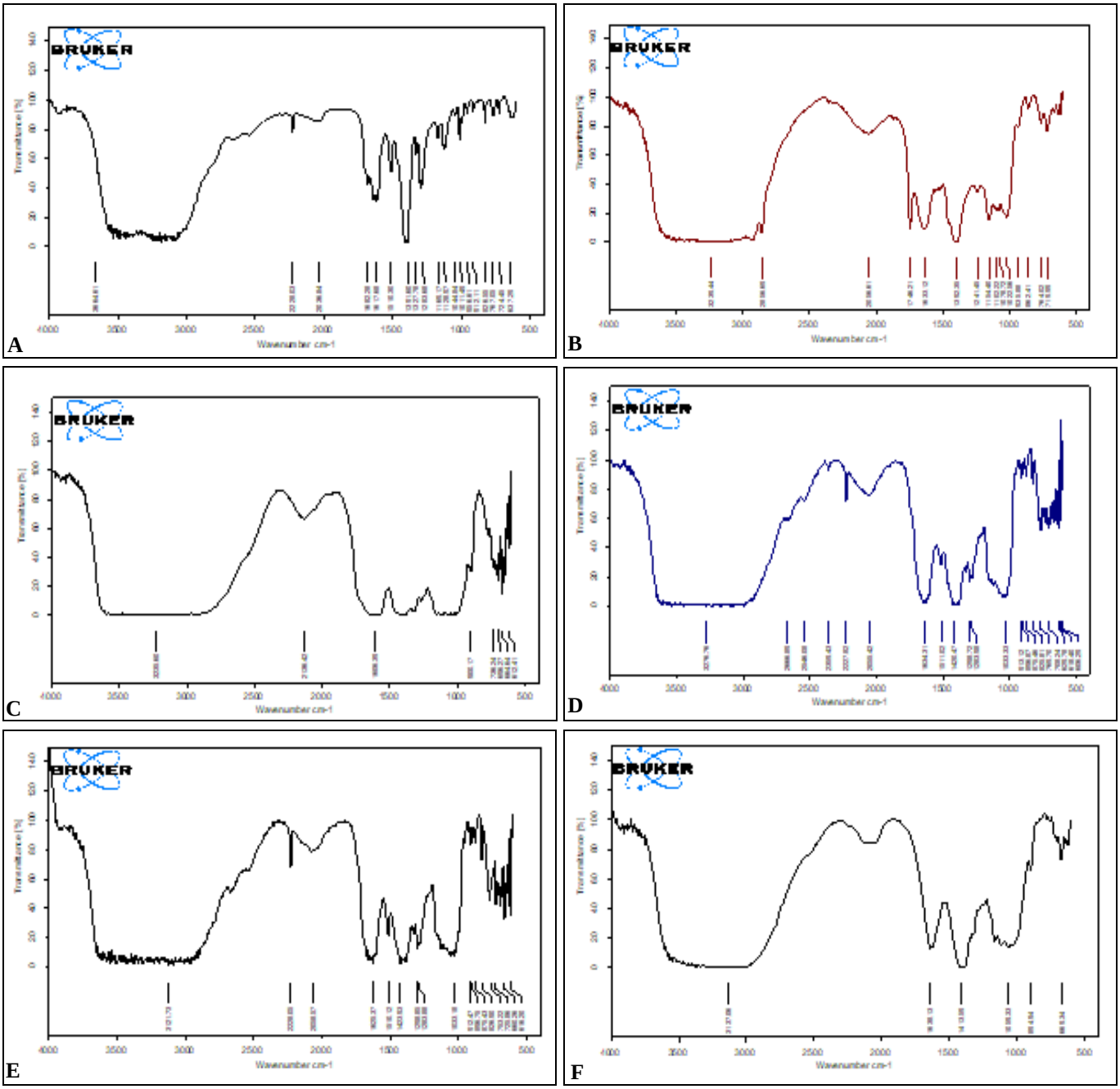

FIG. 5: FT-IR SPECTRA: (A) FEBUXOSTAT PURE DRUG (B) SFS2 (C) CCS (D) FS6 (E) FSL5 (F) FS12

DSC Thermograms: The DSC thermographic studies were carried out on Febuxostat pure drug, SFS2, CCS, fast-dissolving formulations of Febuxostat FS6, FS12 and lyophilized fast dissolving formulation FSL5. These studies exhibited broad endothermic peaks at 217.42 ºC, 266.29 ºC and 303.83 ºC for Febuxostat pure drug, broad exothermic peaks at 340.74 ºC, 354.13 ºC and broad endothermic peaks at 372.41 ºC and 382.42 ºC for SFS2, a sharp exothermic peak at 319.1 ºC for CCS, broad endothermic peaks at 219.42 ºC and 241.27 ºC and a sharp endothermic peak at 238.79 ºC for FS6, broad endothermic peaks at 201.31 ºC, 332.71 ºC, 361.71 ºC, 367.7 ºC, a broad exothermic peak at 309.51 ºC, a sharp endothermic peak at 351.40 ºC and a sharp exothermic peak at 387.04 ºC for FSL5. A sharp endothermic peak at 270.12 ºC, a broad endothermic peak at 312.82 ºC and a sharp exothermic peak at 376.55 ºC were observed for formulation FS12.

It was observed that there is a slight shift in temperature for drug, SFS2, and CCS in the formulations. The detailed thermographs were shown in **Fig. 6**.

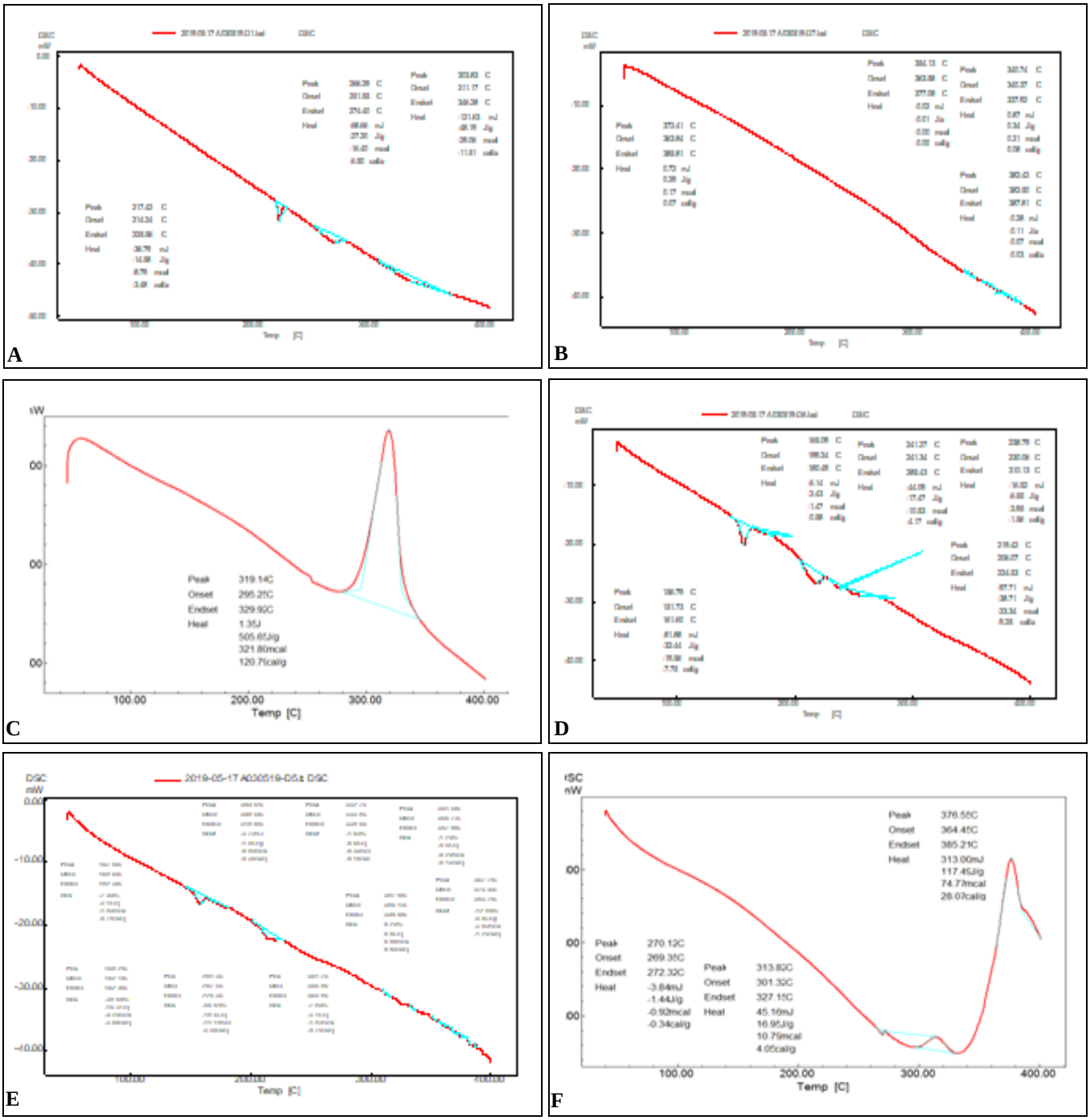

FIG. 6: DSC THERMOGRAMS: (A) FEBUXOSTAT PURE DRUG (B) SFS2 (C) CCS (D) FS6 (E) FSL5 (F) FS12

SEM Studies: Scanning electron microscopy images were taken for Febuxostat pure drug, SFS2, CCS, a blend of Febuxostat with poloxamer-188, Febuxostat with SFS2 and lyophilized product of Febuxostat with SFS2.

Febuxostat pure drug exhibited crystalline form. The SFS2 starch exhibited a free-flowing spherical low, dense form of starch grains without any mucilage/resinous coverage. CCS exhibited blunt tubular-shaped crystals.

The SEM image of Febuxostat with SFS2 exhibited uneven dispersion of drug with spherical globular starch grains. The SEM image of the lyophilized product of Febuxostat with SFS2 showed complete dispersion of drugs with starch.

The SEM image of Febuxostat with CCS showed uniform dispersion of drug with blunt tabular crystals of CCS. The detailed SEM images were shown in **Fig. 7**.

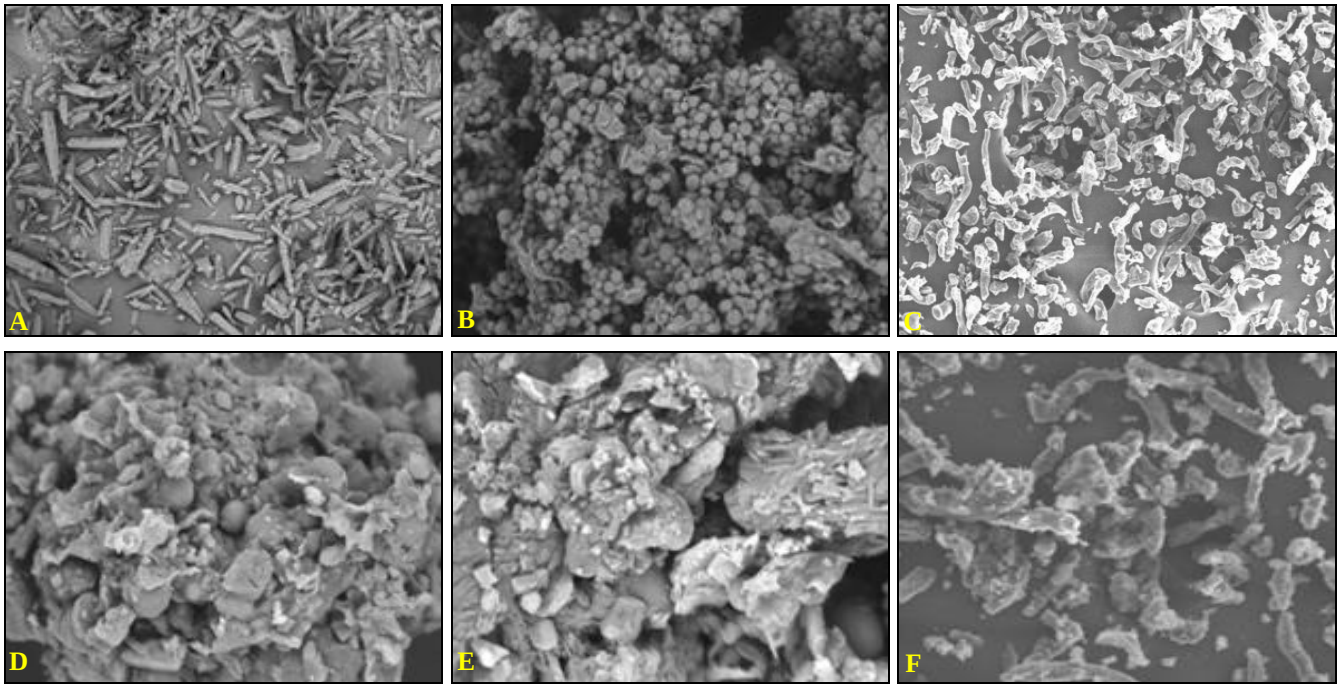

FIG. 7: SEM IMAGES: (A) FEBUXOSTAT PURE DRUG (B) SFS2 (C) CCS (D) A BLEND OF FEBUXOSTAT WITH SFS2 (E) LYOPHILIZED PRODUCT OF FEBUXOSTAT WITH SFS2 (F) A BLEND OF FEBUXOSTAT WITH CCS

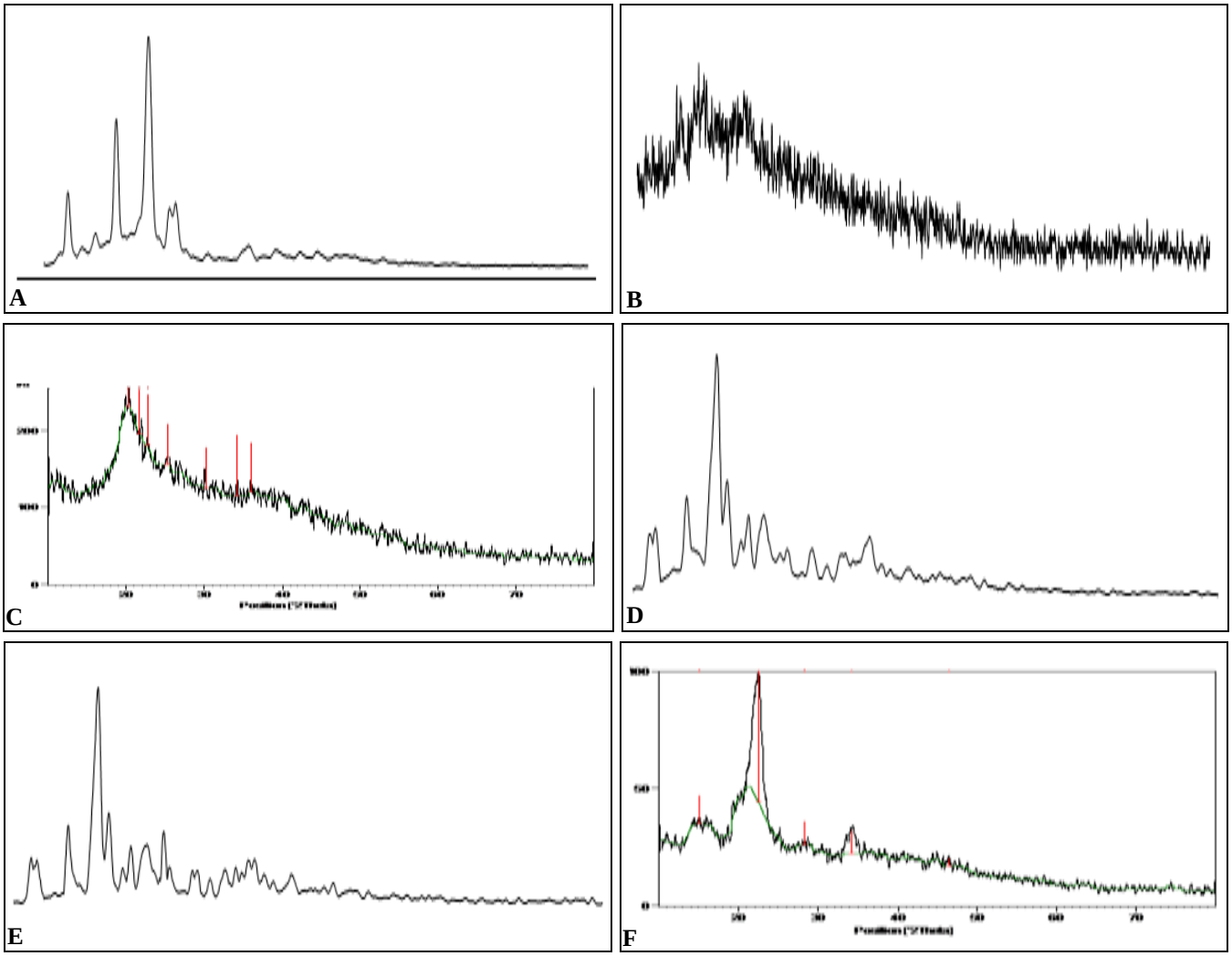

FIG. 8: XRD DIFFRACTOGRAMS: (A) FEBUXOSTAT PURE DRUG (B) SFS2 (C) CCS (D) FS6 (E) FSL5 (F) FS12

X-Ray Diffractograms: XRD diffraction studies were carried out on Febuxostat pure drug, SFS2, CCS, fast-dissolving formulations of Febuxostat FS6, FS12 and lyophilized fast dissolving formulation FSL5. The X-ray diffractogram of Febuxostat showed sharp and intense peaks at diffraction angles (2θ) of 12.082, 25.360 ºC and 26.220 ºC indicating a typical crystalline pattern. SFS2 showed intense peaks at diffraction angles (2θ) of 14.836 ºC, 18.486 ºC, and 23.460 ºC. CCS showed sharp and intense peaks at diffraction angles (2θ) of 21.770 ºC, 22.741 ºC, 25.292 ºC and 30.210 ºC indicating crystalline nature. Formulation, FS6 made with Febuxostat, and 15% w/w of SFS2 showed sharp and intense peaks at diffraction angles (2θ) of 16.440 ºC, 19.868 ºC and 21.168 ºC indicating the disappearance of some of the crystalline peaks of drug and starch. Formulation, FS12 made with Febuxostat, and 15% w/w of CCS showed sharp and intense peaks at diffraction angles (2θ) of 13.024 ºC, 22.547 ºC and 26.334 ºC indicating the disappearance of some of the crystalline peaks of drug and CCS.

Formulation, FSL5, which is a lyophilized product of Febuxostat and 12.5% w/w of SFS2, showed sharp and intense peaks at diffraction angles (2θ) of 16.492 ºC, 19.912 ºC and 21.270 ºC indicating the disappearance of most of the crystalline peaks of drug and starch. This shows the formation of a new solid phase. This suggests the formation of a new solid phase with a lower degree of crystallinity due to complexation. The detailed diffractograms were shown in **Fig. 8**.

CONCLUSION: The current study shows that the proportion of starch as superdisintegrant has greatly influenced the dissolution parameters of various formulations. Similar dissolution profiles were observed for lyophilized formulations, FSL5 containing 12.5% w/w of SFS2, and FSL11 containing 12.5% w/w of CCS as super-disintegrants. The superdisintegrant effect of *Sterculia foetida* seed starch might be due to the rapid uptake of water, followed by swelling that leads to an increase in hydrostatic pressure of tablet that ultimately disintegrates tablets faster. The optimized formulations showed no drug-excipient interactions when subjected to FTIR and DSC analysis. Similarly, crystallinity was observed using XRD studies.

Based on the above studies, it was concluded that lyophilized fast-dissolving formulations of Febuxostat prepared by *Sterculia foetida* seed starch extracted from 0.1% sodium hydroxide showed rapid drug release.

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