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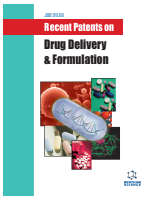
RESEARCH ARTICLE

Formulation and *in vitro* Evaluation of Fast Dissolving Tablets of Febuxostat Using Co-Processed Excipients



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Abstract: ***Background:*** Febuxostat is a novel, orally-administered, powerful, non-purine, xanthine oxidase inhibitor used for treating gout and ceaseless tophaceous gout. The drug exhibits low bioavailability (about 49%) which is ascribed to its dissolution rate-limited absorption.

Objective: The current work is aimed to provide a novel strategy to improve the dissolution profile and thus, the bioavailability of Febuxostat.

Methods: Formulation of Fast Dissolving Tablets (FDT) is anticipated to provide immediate release of the drug, which in turn, will improve its dissolution profile to provide the initial surge in plasma concentration required in an acute gout attack. Incorporation of co-processed excipients in a tablet is known to improve the compressibility and disintegration characteristics of the tablets, which, in turn, result in enhanced *in vitro* drug release and improved bioavailability. A combination of crospovidone (it rapidly wicks saliva into the tablet to create the volume development and hydrostatic weight important to give quick disintegration) and microcrystalline cellulose (a highly compressible ingredient with good wicking and absorbing capacity) was, therefore, used as co-processed excipients.

Results: The tablets were prepared by direct compression technique with the application of a 3^2 randomized full factorial design. The prepared tablets were able to release more than 80% of the drug within 10 minutes of the start of dissolution testing and were able to show a better drug release profile in comparison to available marketed formulation.

Conclusion: So, it can be concluded that the developed fast release formulation was found to exhibit convincing *in vitro* results and may prove a boon in the treatment of acute gout attack after establishing *in vivo* potential.

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1. INTRODUCTION

Pharmaceutical excipients are the substances other than the active drug ingredients included in any formulation. In a drug delivery system, excipients either aid in the processing of the system during manufacture or protect/support and/or improve stability, bioavailability, and/or patient acceptability. They also assist in product identification or strengthen other attributes of overall effectiveness and safety of the drug product during its storage and use [1]. When two or more established excipients are mixed in a particular ratio, co-processed excipients are formed. Co-processing of excipients results in the formation of excipient granulates with superior properties in comparison to the individual ingredient or physical mixtures of ingredients.

Co-processing has emerged as an interesting approach which involves preparation of multifunctional excipients in a special way in which physical modification takes place with no alteration in their chemical structure and/or stability. It has been developed primarily to overcome the issues of poor flowability, compressibility, and disintegration potential, with filler-binder combinations being the most frequently tried combinations [1, 2].

International Pharmaceutical Excipient Council (IPEC) defined co-processed excipients as "a combination of two or more compendial or non-compendial excipients designed to physically modify their properties in a manner not achievable by simple physical mixing, and without significant chemical change" [3].

To obtain a product with improved functionality/price is the main aim of co-processing. The exact mechanism that happens during the co-processing procedure is yet to be explored fully, but the outcome of co-processing is a particulate product having an intimate association of all the components with each other which cannot be achieved practically through simple dry blending of components. A co-processed directly compressible adjuvant starts developing with the

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selection of suitable excipients and their targeted proportion to be combined, selection of preparation technique to achieve an optimized product having desired physicochemical parameters and ends up with minimized variations amongst batches [1].

Gout is an arthritic condition in which chronic elevation of uric acid level above the saturation point takes place as a result of the deposition of monosodium urate crystals in the joints [4]. In the chronic form, the end product of purine metabolism *i.e*. microscopic/macroscopic soft tissue deposits of monosodium urate crystals (tophi) usually gets deposited in and around the joint that leads to bone and joint destruction. It triggers a severe, but self-limiting acute attack of arthritis with an intense pain [5]. Gout usually appears as a part of a complex condition associated with metabolic syndrome, heavy alcohol intake, hypertension, use of diuretics and renal impairment [4]. Gout is characterized by chronic hyperuricemia which is characterized by serum urate levels exceeding 6.8 mg/dl (≥ 400 μmol/L), the level beyond which the physiological saturation threshold is exceeded. Three major types of gout are reported (Fig. **1**).

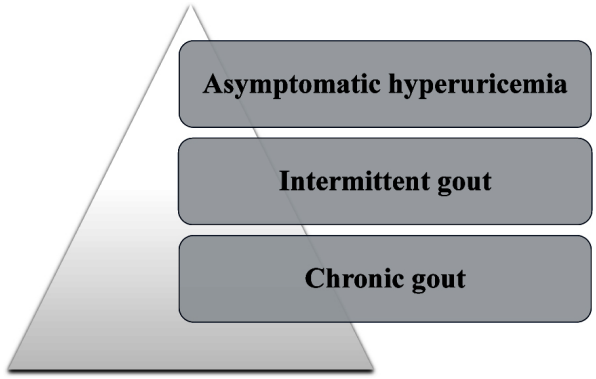


Fig. (1). Types of Gout. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

In 2014, Dalbeth and Stamp modified this staging and proposed four stages, where the period of asymptomatic hyperuricemia has been subdivided into 2 separate stages: Stage A (hyperuricemia without any detectable monosodium urate crystal deposition); Stage B (hyperuricemia with monosodium urate crystal deposition without any signs/symptoms of gout); Stage C (deposition of monosodium urate crystal with prior or current symptoms of a gout flare); and Stage D (advanced gout which needs a specialist's intervention) [6].

The model drug selected for the present work is Febuxostat which is a novel selective inhibitor of xanthine oxidase (non-purine) [7]. It is usually metabolized by the liver while renal elimination has a minor role. Febuxostat is given orally as a 40 mg/day dose. However, it may be increased to 80 mg and then to 120 mg/day after 2 weeks if the target level is still not achieved.

As a non-competitive xanthine oxidase inhibitor (XOI), Febuxostat appears to be superior over the competitive XOI allopurinol, owing to its greater potency, specificity and a decreased reliance on renal excretion. It has been shown to be better than fixed-dose (300 mg) allopurinol in terms of its efficacy as a urate-lowering agent [8].

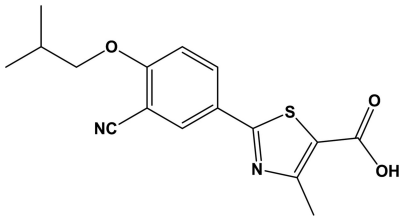


Fig. (2). Chemical structure of Febuxostat.

Febuxostat exhibits poor bioavailability of about 49% which is attributed to its poor solubility [9]. The major drawback of the currently available formulations (film coated tablets) is their low bioavailability due to dissolution rate-limited absorption. The purpose of the present work is to provide a novel way to improve the dissolution and bioavailability of Febuxostat (Fig. **2**). Formulation of fast dissolving tablets may provide a faster release of the drug so as to improve its dissolution rate.

2. MATERIAL AND METHODS

2.1. Materials

Febuxostat was received as a gift sample from Ami Lifesciences Pvt. Ltd., India. Crospovidone was procured from Colorcon Pharmaceuticals, India. All the other excipients were procured from CDH(P) Ltd., India and were of analytical grade.

2.2. Methods of Preparation

2.2.1. Preformulation Study

2.2.1.1. Determination of Melting Point

The capillary method was used for the determination of melting point. A drug filled capillary with was introduced into the digital melting point apparatus. The temperature range during which the test substance melted was noted down [10].

2.2.1.2. Detection of Absorbance Maxima (λ_{max}) of Drug and Preparation of Calibration Curve

Ten mg of accurately weighed Febuxostat was dissolved in pH 6.8 phosphate buffer in a volumetric flask (10 ml). The final volume was made up (concentration 1000 μg/ml) after sonicating for 2 minutes. Further dilutions were made from this stock solution. The samples were scanned on a UV-visible (double beam) spectrophotometer (between 200 to 400 nm). The wavelength at which maximum absorbance (λ_{max}) observed was considered as the analytical wavelength of Febuxostat in the given media [11]. At this wavelength, absorbance values of different dilutions were observed and a calibration curve of the drug was plotted to find out a straight-line equation.

2.2.1.3. Drug Excipients Compatibility Study

The physical mixtures of drug with all the excipients (1:1 ratio) were kept for a period of 1 month at ambient conditions of humidity and temperature. Fourier Transform Infrared (FTIR) analysis was done to obtain information on any possible alteration in physical and/or chemical integrity of drug and/or excipients using KBr pellet in the infrared range of 4000-400cm^{-1} [12].

2.3. Preparation of Co-Processed Excipient

Using the solvent evaporation method, the co-processed excipient of crospovidone and microcrystalline cellulose was prepared. A blend ratio of crospovidone and microcrystalline cellulose (1:1) was added to absolute ethanol. The contents were mixed thoroughly and the solvent was allowed to evaporate until a dough-like mass was formed. The wet coherent mass was granulated by passing through # 44 mesh sieve and dried in a hot air oven (60ºC for 20 min). These granules (dried) were again passed through a sieve (# 44 mesh) and stored in an airtight container until further use [13].

2.4. Evaluation of Co-Processed Excipient

2.4.1. FTIR

The prepared co-processed excipient was subjected to FTIR analysis as mentioned earlier to confirm the chemical integrity of the individual ingredient.

2.4.2. Differential Scanning Calorimetry (DSC)

Possible incompatibilities can be quickly evaluated with DSC since it shows exothermic/endothermic peaks as well as variations in the corresponding enthalpies of reaction. Individual excipients and co-processed excipient were recorded with their DSC thermograms at a heating rate of 100ºC/min over a temperature range of 40ºC to 300ºC [14].

2.5. Pre-Compression Evaluation

2.5.1. Angle of Repose

The angle of repose (θ) of powder blends was determined using the funnel method. The diameter of the powder cone was measured and θ was calculated [15] using the formula-

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

where, 'h' and 'r' are the height of pile and radius of the base of pile, respectively [16]. The determination was carried out in triplicate.

2.5.2. Bulk Density

It is the ratio of total mass to the bulk volume of the given powder. The bulk density was calculated using the below-given formula [14]. Three determinations were performed.

$$\text{Bulk density} = M/Vo \ldots\ldots \quad (2)$$

2.5.3. Tapped Density

It is the ratio of the total mass to the tapped volume of powder. A measuring cylinder having a known mass of powder was tapped (100 times) and volume was measured after tapping. The minimum volume (V_t) occupied in the cylinder and weight of powder blend (M) were measured. A reported formula was used to calculate the tapped density [17]-

$$\text{Tapped density} = M/V_t \ldots\ldots \quad (3)$$

2.5.4. Carr's Compressibility Index

Compressibility index, the simplest way of measurement of the free flow of powder, indicates the ease with which a material can be induced to flow (Carr's Compressibility Index). The % compressibility can be calculated by multiplying the ratio of the difference between tapped density and bulk density to tapped density with 100 [18]. The determination was performed in triplicate.

Carr's Compressibility Index = 100 X ((tapped density-bulk density))/ (tapped density) …… (4)

2.5.5. Hausner's Ratio (HR)

HR is an indirect index of the ease with which a powder flows. The lower the value of Hausner's ratio, the better is the flow property. HR was calculated using the following formula [18].

HR = (tapped density)/ (bulk density)…… (5)

2.6. Optimization of Formulation Using 3^2 Factorial Design (FD)

A randomized full factorial design (3^2) was applied in the present study for optimization of the best formulation. The factorial design involved evaluation of 2 factors, each at 3 levels and execution of experimental trials at all 9 possible combinations. The design facilitated the study of the effect of co-processed excipient combination of crospovidone-microcrystalline cellulose (X1) and mannitol (X2) at 3 different levels *i.e.* low (-1), medium (0) and high (+1), on disintegration time and *in vitro* drug release of prepared formulations as dependent variables [13]. Lactose was used as a bulking agent to maintain the uniformity of tablets' weight throughout all the batches.

2.7. Preparation of Febuxostat Fast Dissolving Tablets

Fast dissolving tablets of Febuxostat were prepared by direct compression technique, incorporating co-processed excipient of crospovidone and microcrystalline cellulose, mannitol, magnesium stearate, talc, and lactose. All the ingredients were weighed and passed through a sieve (#60 mesh) separately. These ingredients were then mixed in a geometrical order to compress into tablets of 230 mg individual weight, using a 12-station rotary tablet compression machine [16]. Twelve formulations were designed, one of which was a control (DF-0) and two others (C-1&C-2) were prepared as checkpoints. The composition of all formulations is given in Table **1** below.

2.8. Post Compression Evaluation

All batches of tablets were evaluated for various quality parameters like the uniformity of weight, hardness, % friability, disintegration time, water absorption ratio, time of wetting, *in vitro* drug release study and kinetics of drug release.

2.8.1. Hardness

Tablet hardness is the force with which a tablet is broken in a diametric compression by using Monsanto hardness tester. The test was performed on 6 tablets of each batch and the average hardness was calculated [13, 18].

2.8.2. Friability

The weight of 10 tablets from each batch was observed on an electronic balance. The tablets were then put in the

Table 1. Composition of formulations (3^2 full factorial design).

Ingredients (mg)	Formulation Code											
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	C-1	C-2	DF-0
Drug	40	40	40	40	40	40	40	40	40	40	40	40
Mannitol	130	130	130	120	120	120	110	110	110	115	125	130
Co-Processed excipient	30	20	10	30	20	10	30	20	10	15	25	-
Lactose	5	15	25	15	25	35	25	35	45	35	15	35
Mg stearate	15	15	15	15	15	15	15	15	15	15	15	15
Talc	10	10	10	10	10	10	10	10	10	10	10	10
Total weight	230	230	230	230	230	230	230	230	230	230	230	230

revolving drum (25 rpm) of a Roche's friabilator which subjected the tablets to rolling and repeated shock that resulted from free-fall within the apparatus. After 4 min, the tablets were taken out, de-dusted and reweighed. The weight was then noted and friability was calculated as % loss in weight. Each experiment was performed in triplicate [12].

2.8.3. Weight Variation Test

This test was performed by sampling and weighing 20 tablets at random from each batch and the average weight was calculated [19, 20].

2.8.4. Disintegration Time

A tablet was put in a beaker having 20 ml of distilled water maintained at 37±0.5°C. The time taken for the complete disintegration of the tablet was noted down in triplicate [18, 21].

2.8.5. Wetting Time and Water Absorption Ratio

The wetting time of the tablets was measured using a simple procedure. A filter paper (10 cm diameter) was placed in a petri dish having a diameter of 10 cm. One milliliter of amaranth (a water-soluble dye) solution was added to a petri dish. A pre-weighed tablet was carefully placed on the filter paper. The time taken by water to reach the upper surface of the tablet was noted as a wetting time. The wetted tablet was then reweighed for determination of water absorption ratio using the formula:

$$R = (wa\text{-}wb)/ wb*100 \ldots\ldots \quad (6)$$

where 'wb' and 'wa' are tablet weights before and after water absorption, respectively. Three determinations were performed for each sample [15, 22].

2.8.6. In vitro Drug Release Studies

In vitro release performance of the fast disintegrating tablets was evaluated in USP type II dissolution apparatus with a paddle stirrer rotating at 75 rpm using 900 ml of phosphate buffer (pH 6.8) as a dissolution medium at a temperature of 37°±0.5C. Aliquots of 5 ml samples were withdrawn at specified time intervals (0, 5, 10, 15, 20, 30, 6, 8, 10, 15, 20, 30 min) and replaced with an equal volume of fresh medium. The withdrawn samples were analyzed for drug content spectrophotometrically at λ_{max} of 312 nm. The concentration of drug was calculated and was expressed as a cumulative % of the drug released. The test was performed in triplicate [17].

2.8.7. Drug Release Kinetics

To characterize the drug product, ensure batch-to-batch reproducibility and consistent pharmacological/biological activity, an appropriate drug release test is necessary to carry out. To determine the mechanism of drug release, the obtained dissolution data were subjected to various drug release kinetic models viz. zero-order model, 1st order rate, Korsmeyer-Peppas model, Higuchi model, and Hixon-Crowell [23]. The coefficient of determination ($R^2 \geq 0.99$) for each model was calculated.

3. RESULTS AND DISCUSSION

3.1. Melting Point

Melting point of Febuxostat was found to be in a range of 206° to 208°C which was in agreement with the available literature [24].

3.2. Detection of λ_{max} of Drug and Preparation of Calibration Curve

When the drug solution was examined in the range 200 nm to 400 nm, the solution showed absorption maxima at about 312 nm [25].

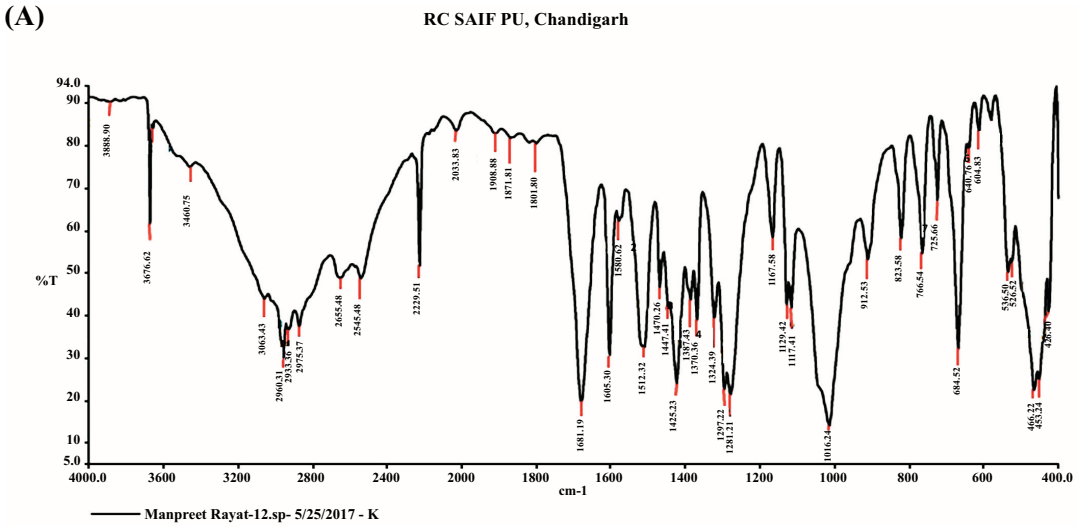
The calibration curve was plotted between the concentration and absorbance. The square of the regression coefficient (R^2) was found to be 0.9995 showing a good amount of correlation.

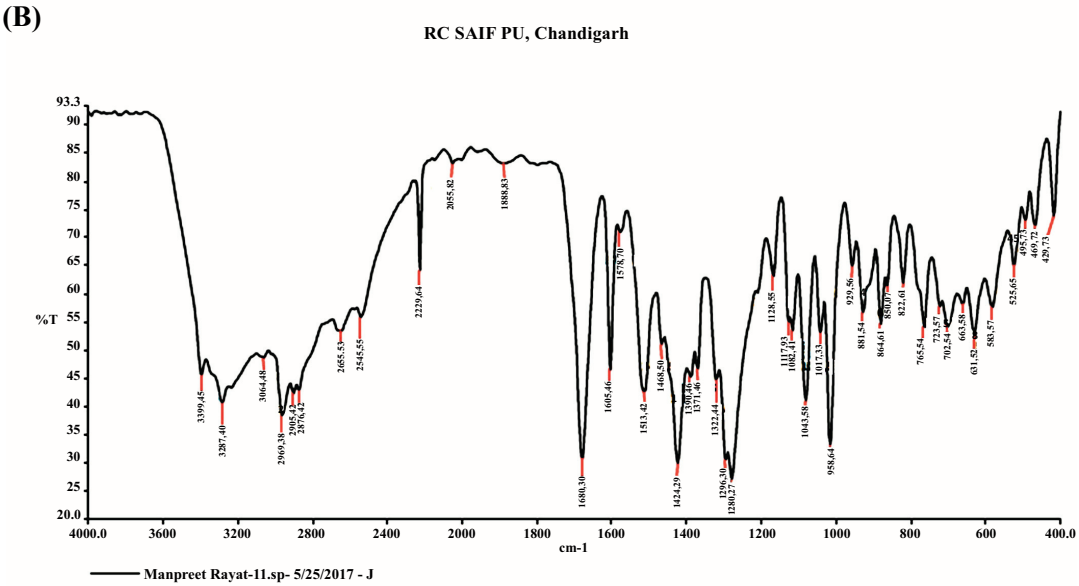
3.3. Drug-Excipient Compatibility Study

FTIR study was undertaken to assess the drug excipient interaction. The FTIR spectra of Febuxostat and excipient mixtures are shown in Figs. (**3** and **4**). The spectrum of pure drug presented characteristic bands at 3546.97 cm^{-1} (O-H stretching); 2938.41, 2959.35cm^{-1} (C-H stretching); 1680.21 cm^{-1} (C-O stretching); 1512.33,1579.63 cm^{-1} (C-C stretching) respectively [26] (Table **2**).

Table 2. Bands observed in FTIR spectra of drug and excipient mixture.

Ingredient	Functional Group				
	C=O	C=C	C-H	O-H	C≡N
Drug (Febuxostat)	1681.21	1512, 1579	1425	3546	2229
Drug + Mannitol	1680.3	1513, 1578	1424	-	2229
Drug + MCC	1681	1512,1580	1425	-	2229
Drug + Crospovidone	1681.23	1511.43	1425.29	-	2229.6
Drug + co-processed excipient	1681	1511, 1580	1425	-	2229
Drug + Magnesium stearate	1681	1523,1578	1425	-	2229.5
Drug + Talc	1681	1512,1579	1425	-	2229
Drug + Lactose	1680.2	1514.32, 1579.61	1425	3525.52	2229.55
Drug + All excipients	1681	1577	1425	3523	2229





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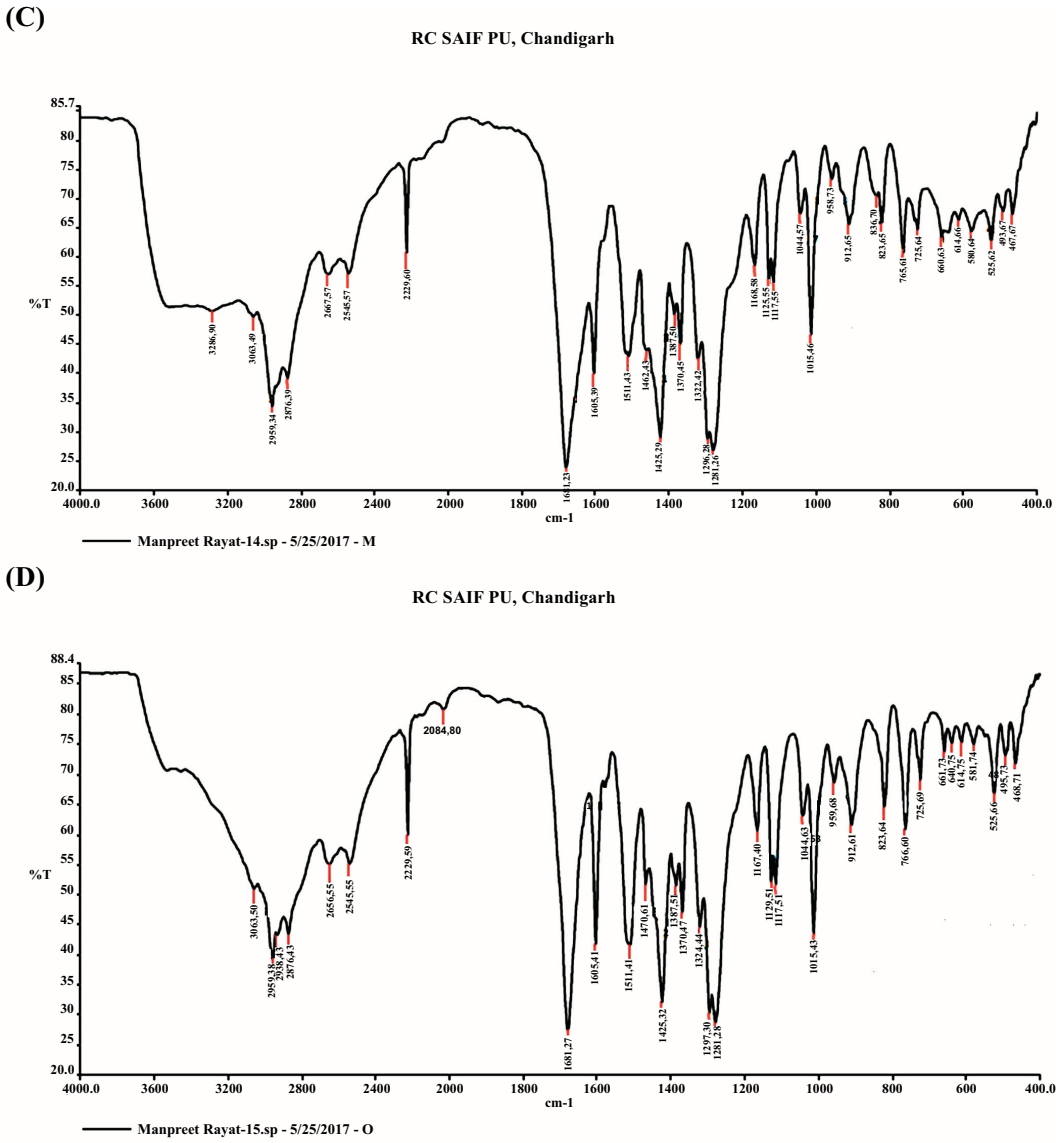


Fig. (3). FTIR spectrum of the physical mixture (**A**) Drug: Talc; (**B**) drug: Mannitol; (**C**) Drug: Crospovidone; (**D**) drug: Co-processed excipient. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The characteristic bands of pure Febuxostat were found to be in the physical mixture of Febuxostat with each excipient and a combined mixture of Febuxostat with all excipients. From the observed data, it was inferred that the drug was compatible with all the excipients. Furthermore, the co-processed product did not show any chemical interaction with Febuxostat, ensuring compatibility.

3.4. Evaluation of Co-Processed Excipient

3.4.1. Flow Properties

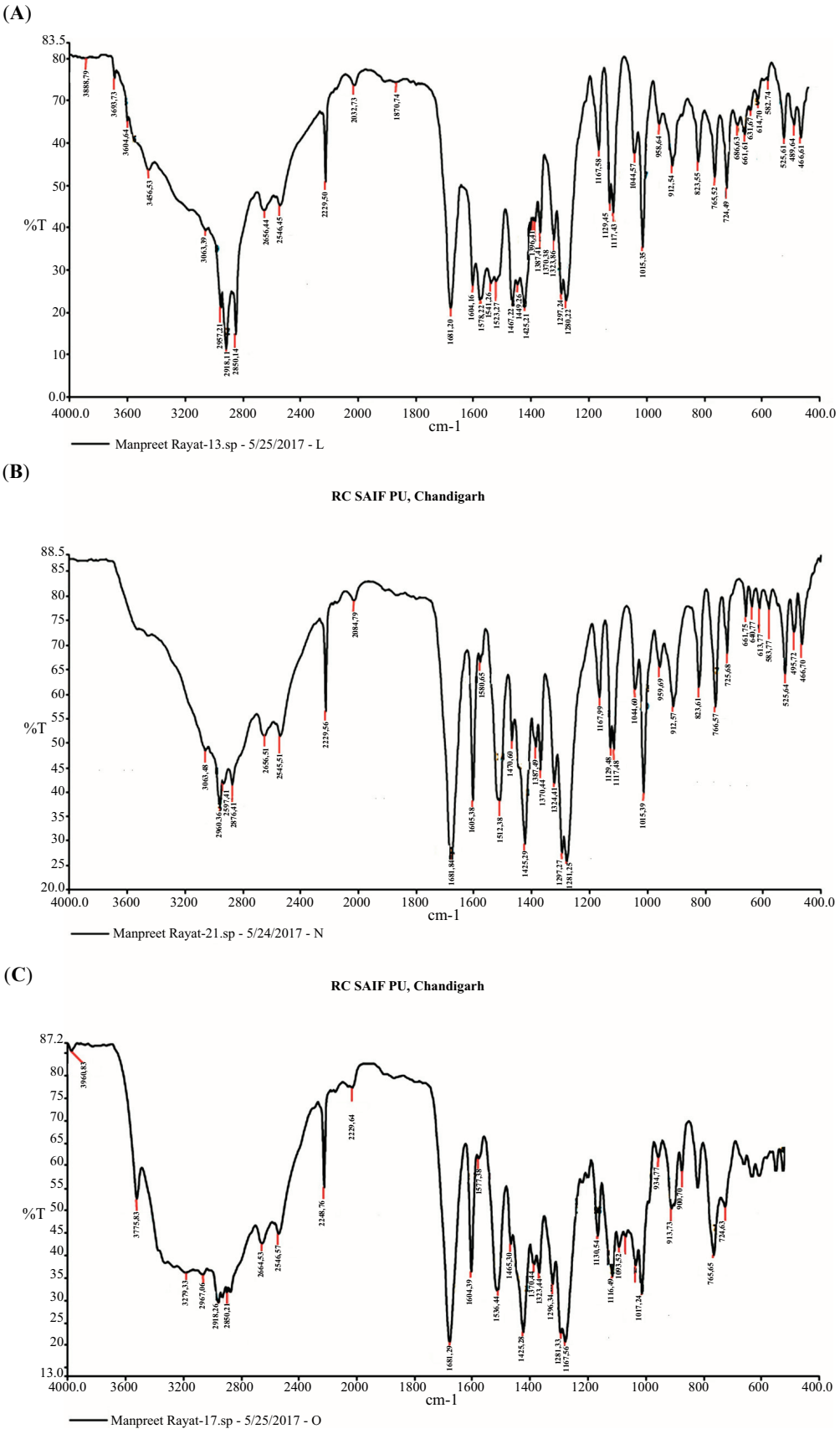
A co-processed excipient was evaluated for its flow and compression properties. The angle of repose of co-processed excipient was found to be <30, which indicated a good flow. The values of Carr's index and Hausner's ratio were also appreciably less with the co-processed excipient (Table **3**), indicating good flowability.

3.4.2. FTIR Study

FTIR spectra of crospovidone, microcrystalline cellulose PH 102, and co-processed excipient did not exhibit any noticeable variation and/or shift in the characteristic absorption bands, suggesting the absence of any chemical interaction between crospovidone and microcrystalline cellulose PH 102 during the process. This confirmed the compatibility of the ingredients involved therein (Figs. **5** and **6**), (Table **4**).

3.5. Post Compression Parameters

Febuxostat fast dissolving tablets were prepared by direct compression method. Tablets were found to be of uniform weight with acceptable variation as per IP specifications. All the formulations were found to possess hardness in a range of 3.5-4.5 kg/cm^2 as compared to 5 kg/cm^2 of controlled batch formulation which aided in faster disintegration of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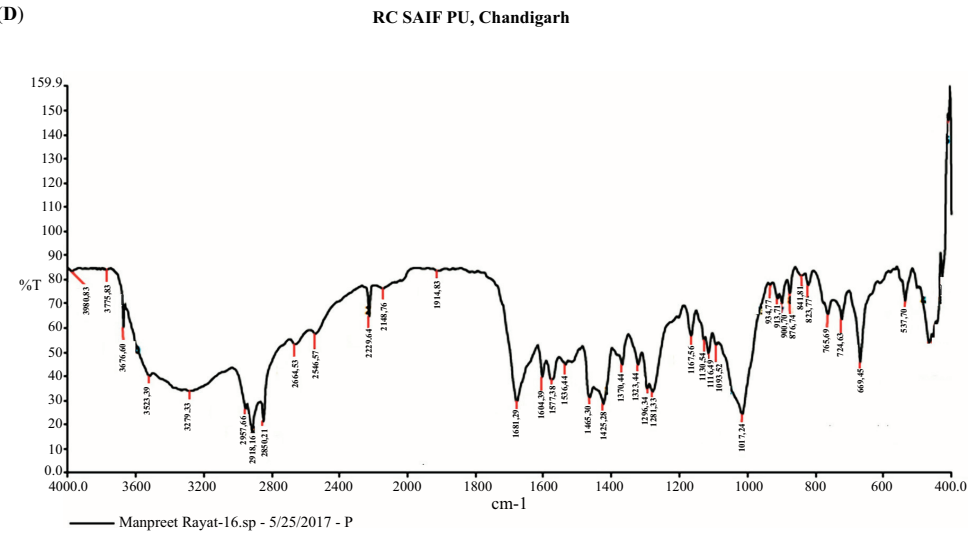
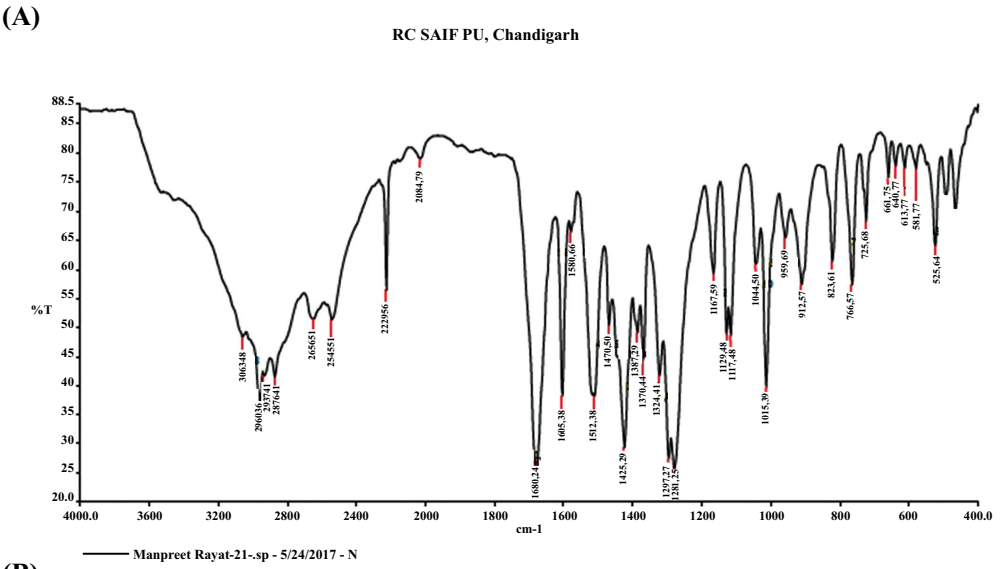
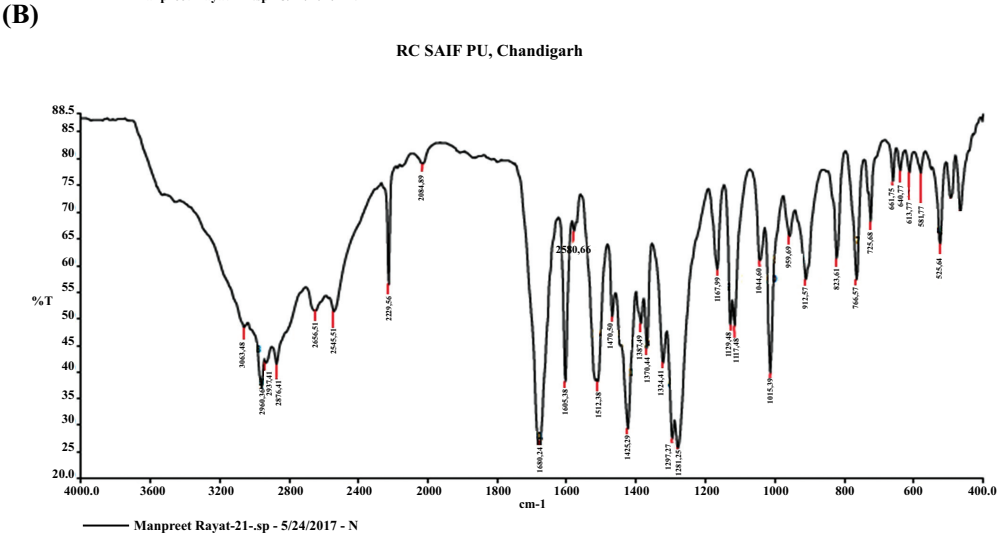


Fig. (4). FTIR spectrum of physical mixture (**A**) Drug: Magnesium Stearate; (**B**) Drug: Microcrystalline Cellulose; (**C**) Drug: Lactose; (**D**) Drug: All Excipients. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).





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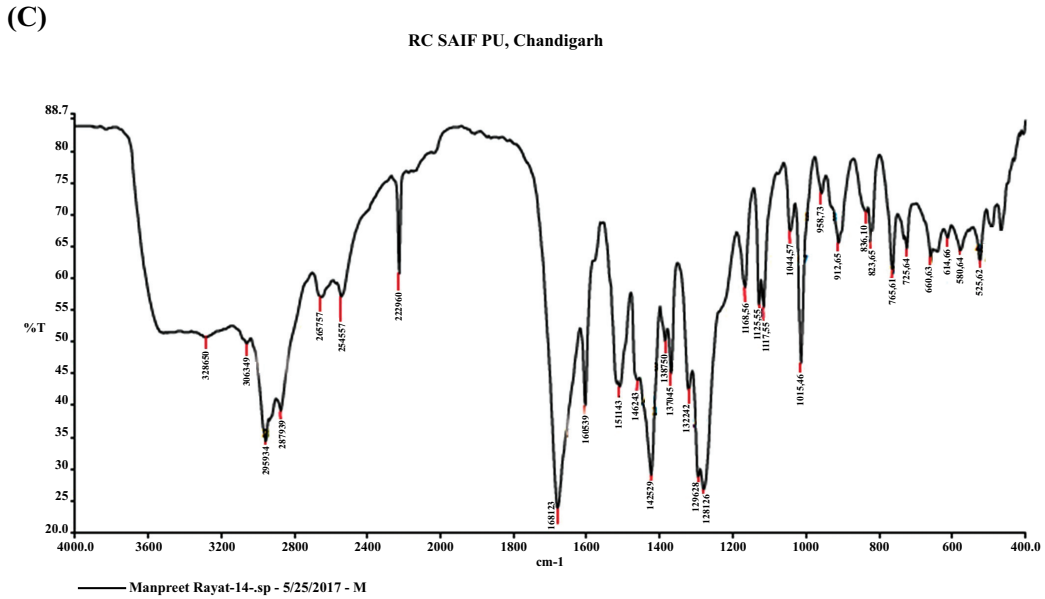

Fig. (5). FTIR spectrum of (**A**) Microcrystalline cellulose; (**B**) Crospovidone; (**C**) Co-processed excipient. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

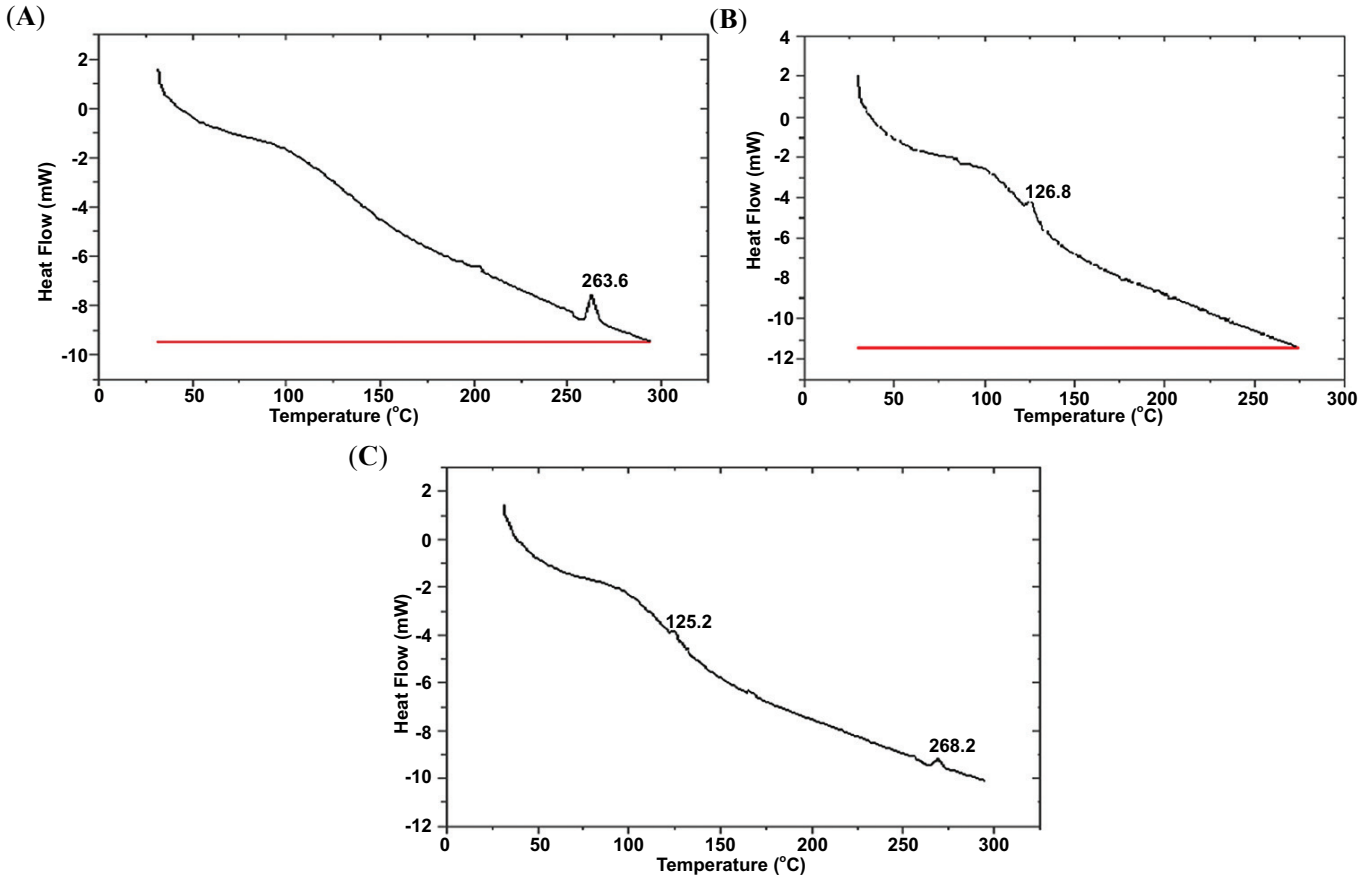

Fig. (6). DSC thermograph of (**A**) MCC; (**B**) Crospovidone; (**C**) Co-processed excipient. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 3. Flow properties of co-processed excipient.

Parameters	Results
Bulk density*	0.174±0.01
Tapped density*	0.205±0.03
Angle of repose	26°
Carr's index	13.75
Hausner's ratio	1.15

*Average values of three readings± SD.

Table 4. Precompression evaluation.

Parameter	Formulation code											
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	DF-0	C-1	C-2
Bulk density	0.23±0.01	0.59±0.09	0.314±0.06	0.27±0.08	0.56±0.32	0.54±0.22	0.57±0.12	0.19±0.05	0.52±0.07	0.22±0.01	0.43±0.04	0.49±0.05
Tapped density	0.61±0.13	0.69±0.14	0.63±0.15	0.60±0.17	0.67±0.12	0.64±0.19	0.65±0.15	0.23±0.01	0.61±0.06	0.35±0.07	0.54±0.03	0.59±0.04
Angle of repose	28	26	27	30	31	30	27	31	27	40	29	27
Carr's index	17.56	14.49	16.5	18.2	16.4	14.91	12.30	19.24	14.7	23.2	18.3	17.6
HR	1.19	1.16	1.21	1.23	1.19	1.17	1.14	1.21	1.17	1.15	1.14	1.13

formulation without compromising with friability limits. The % friability of all formulations was less than 1, indicating good mechanical characteristics. It was also observed that all formulations (F-1-F-9) showed decreased values of both wetting and disintegration times as compared to the control formulation (DF-0). The decrease in wetting and disintegration times in all formulations may be attributed to the presence of co-processed excipient which absorbed water and swelled up, causing rupture of the tablets. The co-processed excipient produced formulations with superior properties. Crospovidone quickly wicked saliva into the tablet to develop the volume expansion and hydrostatic pressures required to provide rapid disintegration in the mouth. In addition to it, microcrystalline cellulose also would aid in the wicking and absorbing capacity of the formulation [27]. The disintegration time was found to be in the range of 70-120 seconds. This rapid disintegration may assist in swallowing and also play a role in drug absorption in the buccal cavity, thus promoting the bioavailability of the drug. The combined results are shown in Table **5**.

3.6. *In vitro* Drug Release Study

In vitro drug release studies of prepared formulations (F-1-F-9), the control (DF-0) and extra checkpoint formulations (C-1 & C-2) were carried out in pH 6.8 phosphate buffer. It was observed that the use of co-processed excipient increased the dissolution rate as compared to that of the controlled formulation. Formulation with co-processed excipient (F-1-F-9) showed maximum release within 10 minutes as compared to the controlled formulation which showed maximum release at 30 minutes (Fig. **7**). Amongst all the formulations, formulation F-2, F-7 and F-9 were able to achieve more than 80% drug release within the first 10 minutes of the start of the test. All the results were expressed as mean ± SD (standard deviation). The results obtained from the drug release study are summarized in Table **6**.

3.7. Factorial Design

In the current study, a 3^2 full factorial design was utilized to understand the effect of independent variables, *i.e*. the amount of co-processed excipient (X1) and the amount of binder (Mannitol, X2) on dependent variables like disintegration time and *in vitro* drug release. The results as summarized in the table below clearly indicate that all the dependent variables were strongly influenced by the selected independent variables on account of showing a wide variation among the nine batches and two extra checkpoint batches (Table **7**). The validity of this method was verified by designing two extra design checkpoint formulations (C-1 & C-2). The disintegration time values for these formulations were 95 and 90 seconds. The closeness of the predicted values to the observed values for C-1 and C-2 in the method indicates the validity of the derived equation for the dependent variable (disintegration time).

3.8. Selection of Optimized Formulation and its Comparison with Marketed Tablet

Optimized formulations were selected based on disintegration time and *in vitro* drug release profiles of all formulations. Considering these two parameters, the fast dissolving tablets of batch F-2, F-7 and F-9 were selected as optimized formulations amongst all other batches (Fig. **8**). The drug release profile of these optimized formulations was compared with that of commercially available tablets. The results are summarized in Table **8** below.

Table 5. Results of post-compression parameters.

Parameter	Formulation code											
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	DF-0	C-1	C-2
Hardness (kg/cm^2)	4±0.7	4.2±1.2	4.3±1.1	4.2±1.2	3.9±0.7	3.5±1.0	4.4±0.8	4±0.9	4.4±1.1	5±1.4	4.2±1.2	4.4±1.1
Friability (%)	0.39±0.5	0.28±0.4	0.34±0.8	0.41±0.1	0.5±0.2	0.4±0.04	0.24±0.02	0.34±0.03	0.27±0.07	0.6±0.08	0.7±0.01	0.6±0.02
Wetting time (sec)	50±4	45±3	43±2	49±4	52±5	47±2	49±4	56±5	52±3	68±6	47±2	49±4
Water absorption ratio (%)	30±3	32±4	45±5	35±3	32±4	30±3	28±6	27±6	23±5	56±7	32±4	34±5
Disintegration time (sec)	120±4	74±6	110±3	95±3	89±4	90±2	81±5	97±6	90±4	113±4	95±3	90±3

Table 6. Results of *in vitro* drug release study.

Time (min)	Formulation Code* (Percentage Drug Release)											
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	DF-0	C-1	C-2
0	0.11± 0.041	0.52± 0.081	1.04± 0.001	3.02± 0.07	0.65± 0.07	0.74± 0.06	0.40± 0.026	0.75± 0.031	0.14± 0.042	1.9± 0.05	3.4± 0.023	2.4± 0.042
5	70.09± 0.07	72.20± 0.025	64.82± 0.036	62.41± 0.048	55.19± 0.072	59.65± 0.037	66.16± 0.04	62.26± 0.053	55.90± 0.081	1.31± 0.069	66.74± 0.028	67.74± 0.126
10	79.24± 0.13	82.09± 0.143	75.64± 0.079	74.50± 0.129	58.23± 0.085	62.48± 0.019	80.52± 0.019	67.66± 0.109	87.64± 0.038	1.46± 0.071	75.91± 0.081	78.34± 0.061
15	74.92± 0.032	78.81± 0.076	77.48± 0.095	81.67± 0.063	66.63± 0.019	65.70± 0.061	76.06± 0.049	68.32± 0.051	84.90± 0.061	2.39± 0.025	76.04± 0.02	81.95± 0.051
20	75.40± 0.053	71.01± 0.061	80.40± 0.047	77.51± 0.059	64.12± 0.056	66.63± 0.162	73.88± 0.149	69.56± 0.094	80.27± 0.018	3.36± 0.06	74.29± 0.091	80.52± 0.095
30	73.30± 0.017	77.98± 0.084	75.58± 0.127	76.18± 0.023	63.17± 0.17	68.65± 0.049	72.99± 0.091	71.83± 0.061	79.91± 0.103	12.00± 0.142	69.80± 0.025	78.95± 0.038

*average of three readings ± SD.

Table 7. Results of dependent variables.

Formulation Batches	Independent Variables			Dependent Variables
	X1	X2	Disintegration Time (sec)	*In vitro* Drug Release (%)
F-1	1	1	120	79.24
F-2	1	0	74	82.09
F-3	1	-1	110	75.64
F-4	0	1	95	74.5
F-5	0	0	89	58.23
F-6	0	-1	90	62.48
F-7	-1	1	81	80.52
F-8	-1	0	97	67.66
F-9	-1	-1	90	87.64
C-1	-0.5	-0.5	95	75.91
C-2	0.5	0.5	90	78.34

Table 8. Comparison of *in vitro* drug release of optimized formulations with a marketed formulation.

Product	% Drug Release After 10 min
Marketed tablet	65.62
F-2	82.09
F-7	80.52
F-9	87.64

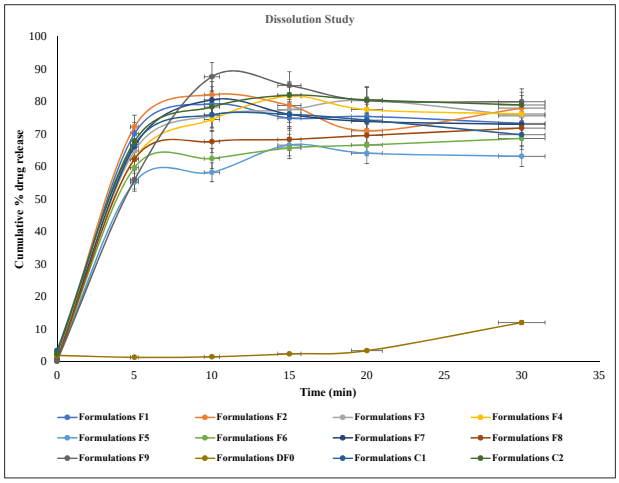

Fig. (7). Cumulative % drug release profile of all formulation batches. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

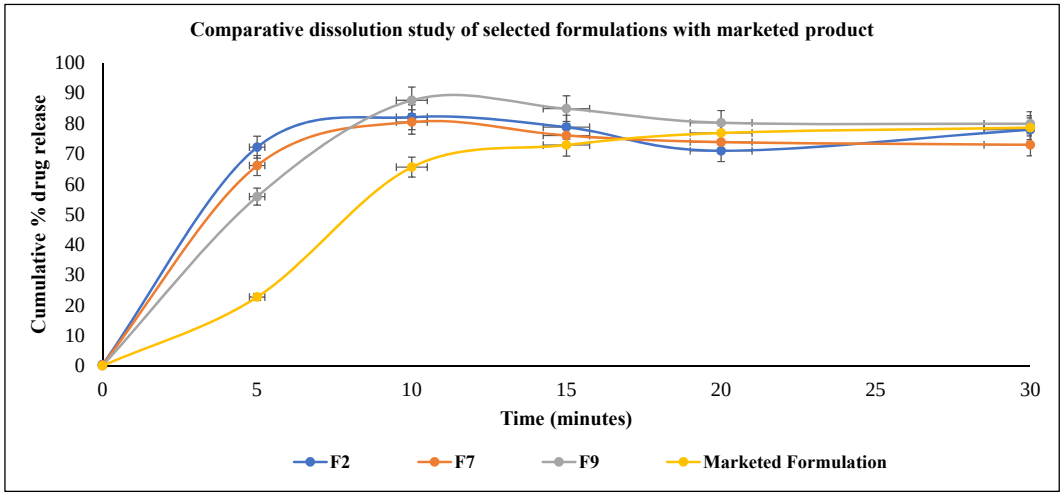

Fig. (8). Comparative release profile of optimized formulations with a marketed tablet. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 9. R^2 values for formulation batches for different mathematical models and 'n' values.

Batch Code	Zero-order		1st order		Higuchi		Korsmeyer-Peppas		Hixson-Crowell	
	R^2	K_0 (h^{-1})	R^2	K_1 (h^{-1})	R^2	K_H ($h^{-1/2}$)	R^2	n	R^2	K_{HC} ($h^{-1/3}$)
F-2	0.838	8.14	0.925	-0.07	0.968	26.92	0.925	2.35	0.894	-0.02
F-7	0.879	8.01	0.966	-0.05	0.985	26.08	0.931	2.45	0.939	-0.19
F-9	0.976	8.79	0.983	-0.09	0.993	27.14	0.946	2.93	0.999	-0.23

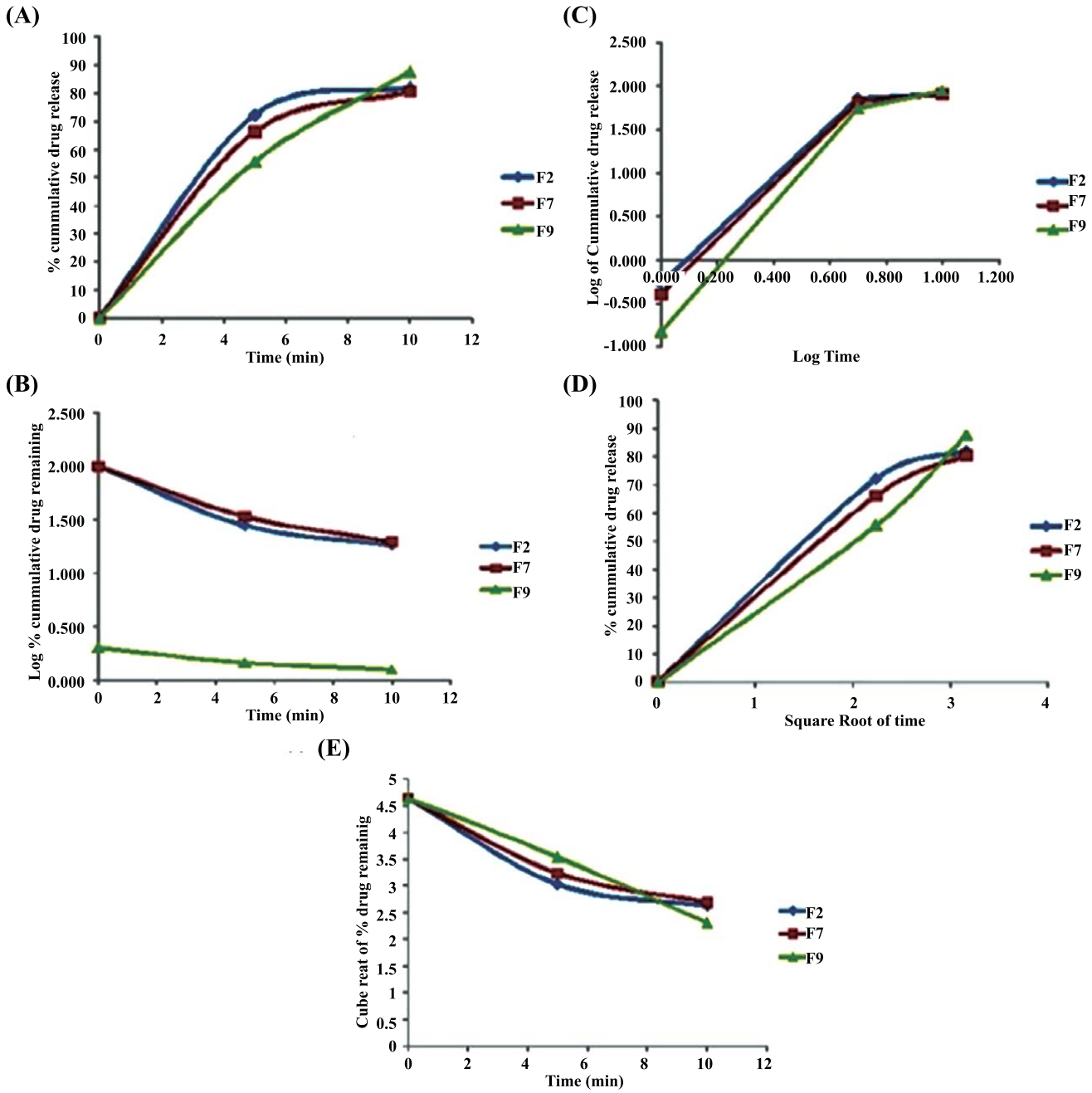

Fig. (9). Drug release kinetic plots of formulations F-2, F-7 & F-9: (**A**) Zero-order; (**B**) 1st order; (**C**) Korsemeyer-Peppas; (**D**) Higuchi; (**E**) Hixson-Crowell. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.9. Drug Release Kinetics (Fig. 9)

The *in vitro* dissolution data of Febuxostat, the fast dissolving tablet formulation, was subjected to the goodness of fit test by linear regression analysis according to zero-order, 1st order kinetic equations, Higuchi's, Korsmeyer-Peppas and Hixson-Crowell models to find out the mechanism of drug release. The results of the analysis are tabulated in Table **9**. Formulations F-2, and F-7 were best fitted to Higuchi's equation, indicating Fickian diffusion for drug release. Formulation F-9 was best fitted to the Hixson-Crowell dissolution model which meant that the change in surface area during the process of dissolution had a significant effect on drug release [28].

CONCLUSION

Fast dissolving tablets of Febuxostat were prepared using a co-processed excipient employing direct compression technique to improve hardness, reduce disintegration time as well as to achieve a better dissolution rate as compared to the commercially available formulation. A co-processed excipi-

ent of crospovidone and microcrystalline cellulose PH 102 in a 1:1 ratio was prepared by the solvent evaporation technique and evaluated for flow properties, DSC, and FTIR. The angle of repose was found to be <30 which indicated good flow. The values of Carr's index and Hausner's ratio were also appreciably less. Results of DSC and FTIR analysis showed the absence of any chemical interaction between ingredients.

Before compression, pre-compression parameters were evaluated using bulk density, tapped density, angle of repose, Carr's index and Hausner's ratio. The powder blends were free-flowing (angle of repose <32° and Carr's index <20%). The values of Carr's index ranged between 12-19, indicating excellent to good flowability.

All batches of tablets were found to show satisfactory results for various post-compression parameters like weight uniformity, hardness, friability, time of disintegration, water absorption ratio, time of wetting and *in vitro* drug release study. All the formulations showed a maximum release ranging from 58 to 88% approximately after 10 minutes, except the controlled formulation (DF-0) where the drug release was appreciably low (< 2%). Out of all the prepared formulations, three formulations were selected as best formulations based on the values of their disintegration time and *in vitro* drug release studies. On comparison of these formulations with the marketed formulation for drug release performance, the developed formulations were found to be superior over the marketed formulation.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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