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Artículos originales

Enhancing the dissolution rate of poorly soluble drug Febuxostat using spray dried amorphous solid dispersion technique

Mejora de la tasa de disolución del fármaco poco soluble Febuxostat utilizando la técnica de dispersión de sólido amorfo secado por aspersión

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Conflict of interest

The authors declare no conflict of interest.

Resumen

Introducción: El febuxostat pertenece a los fármacos clase II del Sistema de Clasificación Biofarmacéutica, los cuales presentan baja solubilidad y alta permeabilidad. La dispersión sólida amorfa es una de las técnicas que pueden ser útiles para mejorar la solubilidad y las características del polvo.

Objetivo: optimizar la concentración de polímeros hidrofílicos e hidrofóbicos para mejorar la velocidad de disolución y la solubilidad de las tabletas de febuxostat.

Métodos: La dispersión sólida amorfa de febuxostat se preparó mediante el método de secado por aspersión utilizando Kolliphor P237 (1:2). Esta dispersión sólida amorfa se utilizó además para comprimir el comprimido. Para mejorar la solubilidad y la tasa de disolución, se aplicó un diseño factorial completo para optimizar la concentración crítica de KollidonSR e hidroxi propil metil celulosa (HPMC K4M). Los comprimidos preparados se caracterizaron por parámetros de precompresión y poscompresión.

Resultados: La velocidad de liberación del fármaco se mantuvo mediante la formulación de una técnica de dispersión sólida amorfa. Se encontró que el lote optimizado (FSRT-OB) era apto para la liberación promedio del 93,30 % del fármaco en forma de liberación sostenida hasta 12 horas. Los datos de la cinética de liberación sugieren que la liberación del fármaco estuvo controlada por una combinación de mecanismo de relajación de cadena y difusión. Se encontró que la concentración optimizada para Kollidon SR y HPMC K4M era 38,50 % y 7,72 % respectivamente.

Conclusión: La técnica de dispersión sólida amorfa es útil para mejorar la solubilidad, la velocidad de disolución y la biodisponibilidad de la tableta de Febuxostat.

Palabras clave: Febuxostat, dispersión sólida amorfa, Kollidon SR, HPMC K4M, diseño factorial completo.

Abstract

Introduction: Febuxostat belongs to Biopharmaceutical classification system (BCS) class II drugs, which have low solubility and high permeability. Amorphous solid dispersion is one of the techniques which can be useful to improve solubility and powder characteristics.

Objective: To optimize the concentration of hydrophilic and hydrophobic polymers to improve the dissolution rate and solubility of febuxostat tablets.

Methods: The amorphous solid dispersion of febuxostat was prepared by spray drying method using Kolliphor P237 (1:2). This amorphous solid dispersion was further used to compress the tablet. To improve solubility and dissolution rate, a full factorial design was applied to optimize the critical concentration of Kollidon SR and hydroxypropyl methyl cellulose (HPMC K4M). The prepared tablets were characterized by pre-compression and post-compression parameters.

Result: The rate of drug release was sustained by formulating an amorphous solid dispersion technique. The optimized batch (FSRT-OB) was found to be fit for release average 93.30 % of the drug in sustain release manner up to 12hrs. The release kinetic data suggests that the drug release was controlled by combination of diffusion and chain relaxation mechanism. The optimized concentration for Kollidon SR and HPMC K4Mwas found to be 38.50 % and 7.72 % respectively.

Conclusion: Amorphous solid dispersion technique is useful to enhance solubility, dissolution rate, and bioavailability of the Febuxostat tablet.

Keywords: Febuxostat, Amorphous Solid dispersion, Kollidon SR, HPMC K4M, Full factorial design

Highlights

The bioavailability of febuxostat is approx. 49 % which is determined by the low dissolution rate of the drug. There is a need to explore another method that can produce amorphous solid dispersion of Febuxostat with minimum residual solvent. There are various techniques used to increase the dissolution rate of the drugs out of that amorphous solid dispersion is one of the powerful techniques to enhance the solubility of the drugs. The successful improvement in the rate of dissolution of febuxostat was obtained by preparing amorphous solid dispersion with Kollidon SR (38.50 % w/w) and HPMC K4M (7.72 %) using the spray drying technique.

Introduction

Febuxostat is used in the treatment of arthritis which targets the xanthine oxidase enzyme. The recommended dose of febuxostat is 40-80 mg per day, administered with or without food. It is mainly used in the treatment of hyperuricemia which is characterized by an increased amount of uric acid due to the breakdown of certain chemical products (purines) in the body[1].These uric acid crystals are accumulated in joints and tissues which can cause gouty arthritis. Febuxostat inhibits the enzyme xanthine oxidase which is responsible for the formation of uric acid crystals from purine-like compounds in the human body. According to the Biopharmaceutical classification system (BCS), febuxostat is classified under class II drugs that possess high intestinal permeability and low aqueous solubility. The bioavailability of febuxostat is approx. 49 % which is determined by the low dissolution rate of the drug.

Dissolution rate can be considered as one of the important parameters, which determine the bioavailability of the drugs across the biological membrane. Approximately, 30-40 % of new chemical entities coming into the market have the problem of poor aqueous solubility. Therefore, improving the solubility and dissolution rate of the poorly soluble drug is one of the most challenging aspects of modern pharmaceutics. There are various techniques used to increase the dissolution rate of the drugs out of that amorphous solid dispersion is one of the powerful techniques to enhance the solubility of the drugs. In this technique, the drug is dispersed throughout the matrix to change drug particles from crystalline to amorphous form with an advantage of particle size reduction[2].

According to the literature review, solvent evaporation and hot melt technique are useful to enhance the solubility and dissolution rate of Febuxostat but these techniques require the use of organic solvents. There is a need to explore another method by which we can produce amorphous solid dispersion of Febuxostat with minimum residual solvent[3]. Spray drying is also an efficient method to obtain the amorphous particles of the drug molecules. Spray drying is the transformation of liquid feed material into solid particulate form by atomization through an atomizer into a hot drying gas medium. The solid particles obtained from the spray drying method show narrow particle size distribution[4].Tablets can be prepared by three techniques; wet granulation, dry granulation, and direct compression[5]. The solid dispersion of febuxostat obtained from the spray drying method can be used to produce a controlled-release tablet of febuxostat[6]. Febuxostat can be mixed with directly compressible excipients to form sustained release dosage form[7].

Full factorial design is response surface design which provides individual effect, combined or interaction effect, and also curvilinear effect. It is an efficient, fast, and convenient method used for optimization study in the pharmaceutical research field[8]. This design is ideal because, in the smaller number of a process run, it can give accurate results. It provides information on experimental variable effects, overall experimental error, and the minimum number of runs required for the optimization study[9]. Therefore, the full factorial design is suitable for formulation optimization of febuxostat tablets prepared using spray-dried amorphous solid dispersion[10]. In this research, we intended to modulate the release kinetics by a combined mechanism: use of the porous structure generated with the insoluble polymer (Kollidon SR) and the other from the hydrophilic gelling polymer (hydroxypropyl methyl cellulose, HPMC grade K4M or hydroxypropyl cellulose, HPC) which imparts slow drug diffusion[11].

Materials and methods

Febuxostat was obtained from Balaji Drugs, Surat, India. The polymers Kolliphor P 237 and Eudragit RLPO were procured from BASF/ Sigma-Aldrich, Bangalore. Silicon dioxide and magnesium stearate were obtained from Loba chemicals/ Durga Scientific, Vadodara. Avicel PH 102 was procured from Astron Chemicals, Ahmedabad. All other ingredients used were of analytical grade[12].

Preparation of amorphous solid dispersion of febuxostat by spray drying method

Solid dispersion was prepared using drug (febuxostat) polymer (Kolliphor P 237) ratio 1:2. The required amount of polymer was weighed and mixed with enough acetone (200 ml) to make a clear solution. Solidification of solid dispersion was done using a spray dryer (Model: LU222 Advance, make: Labulti-

ma), equipped with a high-performance cyclone. The liquid was then atomized in a spray tower using a hollow cone pressure nozzle (bore diameter 0.6 mm) at a pressure of 100 bar. The spray tower was operated with nitrogen at an inlet temperature of 140°C and an outlet temperature of approx. 100 °C. The spray-dried powder was subsequently filtered using a tube filter. Solid dispersion was collected and stored in desiccators. This solid dispersion was further used to produce sustained release tablets of febuxostat[13].

Full factorial design

To optimize the formulation in the minimum number of trials, the screening was done by applying a full factorial design. The full factorial design comprised of; two quantitative factors (X_1, the concentration of Kollidon SR; and X_3, the concentration of hydrophilic polymer) and one qualitative factor (X_2, the type of hydrophilic polymer: HPC or HPMC). The surfaces would be graphical representations of the response as a function of X_1 and X_3, whereas X_2 would be consecutively HPC or HPMC[14]. The Quadratic equations were generated for the measured responses as a function of dependent and independent variables. From the full factorial design run, response surface graphs were generated. For the optimization, 20 batches were prepared by varying the factor levels as shown in Table 1.[15].

Table 1. Full factorial Design set-up for optimization

Sr. No.	Name of Factor	Unit	Level		Remark
			Low	High	
IndependentFactors					
1	Con. of Kollidon SR (X_1)	%	25	40	Insoluble polymer SR polymer
2	Con. of Hydrophilic polymer (X_2)	%	0	10	Hydrophilic, gelling SR polymer
3	Type of Hydrophilic polymer (X_3)	-	HPC	HPMC-K4M	Hydrophilic, gelling SR polymer
4	Drugsoliddispersion	mg	Equivalent to 40 mg of Febuxostat		Drug
5	Silicon dioxide	%	0.5		Flow enhancer
6	Magnesiumstearate	%	0.25		Antiadharent
7	Avicel PH 102	mg	QS (up to 250 mg)		DirectlycompressibleDiluent
Dependent Factor					
1	CDR 2hr (Y_1)	%	-		10- 20 % (15%)
2	CDR 4hr (Y_2)	%	-		21- 30 % (25%)
3	CDR 6hr (Y_3)	%	-		31- 50 % (40%)
4	CDR 8hr (Y_4)	%	-		51-75 % (62.5%)
5	CDR 12hr (Y_5)	%	-		NLT 85 % (>85 %)

CDR: Controlled Drug Release; HPC: hydroxy propyl cellulose; HPMC K4M: hydroxy propyl methyl cellulose, grade K4M; NLT: Not Less Than; QS: Quantity Sufficient.

Total weight of each Tablet is 250 mg. Tablets were compressed using direct compression method, 9 mm standard concave round shaped punch.

Manufacturing of the sustained release solid dispersion tablets

The 120 mg of solid dispersions were mixed thoroughly with the required quantity of Avicel PH 102 using polybag for 10 min. Then 0.5 % of each Aerosil and Magnesium stearate was mixed with the previous blend using polybag for 10 min. The tablets of desired weight (250 mg) were compressed on rotary tablet press by direct compression method using 9 mm standard concave round-shaped punch. Twenty different batches (FSRT1-FSRT20), having a different concentration of sustained-release polymer (Kollidon SR) and different hydrophilic polymer (HPC or HPMC-K4M) were prepared to evaluate the effect of polymer on drug release[2]. The actual composition of all optimization batches is shown in table 2.

Table 2. Actual composition of optimization batches

Batch Code	IndependentFactors			ConstantFactors				Total weight per Tablet (mg)
	Con. of Kollidon SR (mg) (X_1)	Con. of Hydrophilic polymer (mg) (X_2)	Type of hydrophilic polymer (X_3)	SD Equivalent to 40 mg of Febuxostat (mg)	Silicon dioxide (mg)	Magnesium-stearate (mg)	Avicel PH 102 (mg)	
FSRT1	62.5	25	HPMC-K4M	120	1.25	1.25	40	250
FSRT2	62.5	25	HPC	120	1.25	1.25	40	250
FSRT3	100	0	HPC	120	1.25	1.25	27.5	250
FSRT4	81.25	25	HPMC-K4M	120	1.25	1.25	21.25	250
FSRT5	100	12.5	HPMC-K4M	120	1.25	1.25	15	250
FSRT6	81.25	25	HPC	120	1.25	1.25	21.25	250
FSRT7	81.25	0	HPC	120	1.25	1.25	46.25	250
FSRT8	100	25	HPMC-K4M	120	1.25	1.25	2.5	250
FSRT9	81.25	12.5	HPC	120	1.25	1.25	33.75	250
FSRT10	62.5	12.5	HPC	120	1.25	1.25	52.5	250
FSRT11	100	12.5	HPC	120	1.25	1.25	15	250
FSRT12	100	25	HPC	120	1.25	1.25	2.5	250
FSRT13	81.25	12.5	HPC	120	1.25	1.25	33.75	250
FSRT14	81.25	0	HPMC-K4M	120	1.25	1.25	46.25	250
FSRT15	62.5	0	HPMC-K4M	120	1.25	1.25	65	250
FSRT16	81.25	12.5	HPMC-K4M	120	1.25	1.25	33.75	250
FSRT17	100	0	HPMC-K4M	120	1.25	1.25	27.5	250
FSRT18	62.5	12.5	HPMC-K4M	120	1.25	1.25	52.5	250
FSRT19	62.5	0	HPC	120	1.25	1.25	65	250
FSRT20	81.25	12.5	HPMC-K4M	120	1.25	1.25	33.75	250

FSD24: Febuxostat Solid Dispersion containing batch no.24; HPC: Hydroxypropylcellulose; HPMCK4M; Hydroxypropyl methylcellulose K4M.
Total weight of each Tablet is 250 mg; 120 mg of Solid dispersion (FSD24, Drug to polymer ratio 1:2) equivalent to 40 mg of Febuxostat added in each batch. Tablets were compressed using direct compression method, 9 mm standard concave round shaped punch.

Characterization of Tablet containing Febuxostat Solid dispersion

Pre compression tests[16] :

a. Bulk density: The bulk density of a powder mixture is determined by measuring the volume of a known mass of powder sample (Quantity = 20 gm).

b. Tapped density: The Tapped density of a powder mixture is determined by measuring the volume of a known mass of powder sample (20gm) after 100 tapings.

c. Hausner's ratio: It is the ratio of the ease with which powder can flow. Hausner's ratio less than 1.25 indicates good flow property and greater than 1.5 indicates poor flow. To improve the flow property of powder, glidants can be added.

d. Car's index: It is also known as the Compressibility index. By comparing the tapped density and bulk density of the powder, the compressibility of the powder can be determined.

e. Angle of Repose: Angle of repose is defined as the maximum angle viable between the surface of a pile of the powder and the horizontal base.

Post compression tests[16]:

1. Hardness testing

   The hardness of tablets was determined using a Pfizer hardness tester.

2. Weight variation test

   Twenty tablets were selected at random, weighed, and the average weight was calculated. Not more than two of the individual weights should deviate from the average weight by more than 7.5%.

3. Friability test

   For each formulation, a pre-weighed tablet sample (10 tablets) was placed in a friability (Electrolab, Mumbai, India), which is then operated for 100 revolutions. The tablets were de-dusted and reweighed. Compressed tablets that lose not more than 1% of their weight are considered acceptable.

4. Assay

   Twenty tablets were weighed and powdered using glass mortar pestle. The quantity of powder equivalent to 40 mg of febuxostat was accurately weighed and transferred into a 100 ml volumetric flask. Methanol was added up to 100 ml and shaken well. The solution was filtered through a 0.45µ membrane filter. 1 ml of the above solution was transferred into a 100 ml volumetric flask to make up the final volume up to 100 ml using methanol. The absorbance of the resulting solution was measured at a λmax of 315 nm using a UV-Visible spectrophotometer (Shimadzu 1800, Kyoto, Japan). The amount of the febuxostat was calculated by using the equation obtained from the calibration curve.

5. In-Vitro Dissolution study

   In vitro drug release study of prepared batches (n=3) was performed using USP (United States Pharmacopoeia) apparatus II (TDT-08T; Electrolab, India) fitted with a paddle (75 rpm) at 37 ± 0.5°C. In acid stage 750 ml of 0.1M HCL was used as dissolution media. The percentage drug release was calculated up to 2 hrs (Sampling time 0 hr, 1 hr, and 2 hr).

In Buffer stage 0.2 M solution of trisodium phosphate dodecahydrate (Previously warmed up to 36.5°C to 37.5°C, 250 ml) was added to the dissolution basket. To adjust the pH of 6.8 ± 0.05, add 2M hydrochloric acid or 2M sodium hydroxide (if necessary). The sampling was done at the time interval of 4 hr, 6 hr, 8 hr, and 12 hr. At predetermined time intervals, 5 ml samples were withdrawn, filtered through a 0.45µ membrane filter, and analyzed at the respective wavelength (0.1M HCL= 284 nm and buffer stage = 315 nm) using a UV-Visible double beam spectrophotometer (Shimadzu 1800, Kyoto, Japan). Cumulative percentage drug release was calculated using an equation obtained from a calibration curve.

Results and discussion

The powder blends were prepared by mixing all ingredients in a polythene bag. The prepared powder blend of different batches was evaluated for their angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio[17].All results were within acceptance criteria. The post-compression tests were Hardness, friability, and weight variation,they were also found to be satisfactory. The in vitro drug release data for all batches were calculated as shown in table 3.

Table 3. Results of optimization batches (FSRT 1- FSRT 20)

Batch-Code	Independent Factors			Dependent Factors				
	Con. of Kollidon SR (%)	Con. of Hydro-philicpolymer (%)	Type of hydrophilic polymer	% CDR				
				2 hr	4 hr	6 hr	8 hr	12 hr
	X1	X2	X3	Y_1	Y2	Y3	Y4	Y5
FSRT1	25	10	HPMC-K4M	36.08	57.30	89.13	99.49	99.69
FSRT2	25	10	HPC	21.90	40.16	67.54	99.98	100.21
FSRT3	40	0	HPC	2.98	8.37	18.22	27.41	37.91
FSRT4	32.5	10	HPMC-K4M	26.72	42.44	66.02	98.81	101.76
FSRT5	40	5	HPMC-K4M	9.51	17.21	29.72	47.81	65.2
FSRT6	32.5	10	HPC	17.11	31.37	52.76	84.85	99.23
FSRT7	32.5	0	HPC	2.2	8.8	19.6	29.7	41.91
FSRT8	40	10	HPMC-K4M	20.39	32.4	50.51	77.4	101.92
FSRT9	32.5	5	HPC	7.13	17.32	32.65	55.59	78.54
FSRT10	25	5	HPC	8.57	20.81	39.17	66.71	94.25
FSRT11	40	5	HPC	5.96	14.42	27.2	46.33	65.46
FSRT12	40	10	HPC	13.81	25.30	42.55	68.43	94.30
FSRT13	32.5	5	HPC	6.71	16.29	30.68	52.25	73.83
FSRT14	32.5	0	HPMC-K4M	6.11	13.25	26.46	46.8	54.02
FSRT15	25	0	HPMC-K4M	7.5	16.54	33.02	58.6	67.5
FSRT16	32.5	5	HPMC-K4M	12.29	22.53	37.90	60.95	83.99
FSRT17	40	0	HPMC-K4M	5.18	11.32	22.03	38.81	44.87
FSRT18	25	5	HPMC-K4M	16.47	30.20	50.79	81.68	100.02
FSRT19	25	0	HPC	2.60	10.38	23.36	35.05	49.32
FSRT20	32.5	5	HPMC-K4M	12.67	23.23	39.07	62.83	86.59

FSD24: Febuxostat Solid Dispersion containing batch no.24; HPC: Hydroxypropylcellulose; HPMCK4M; Hydroxypropyl methylcellulose K4M
Total weight of each Tablet is 250 mg.120 mg of Solid dispersion (FSD24, Drug to polymer ratio 1:2) equivalent to 40 mg of Febuxostat added in each batch.

The graphical representation of comparative % drug release of all batches is shown in figure 1.

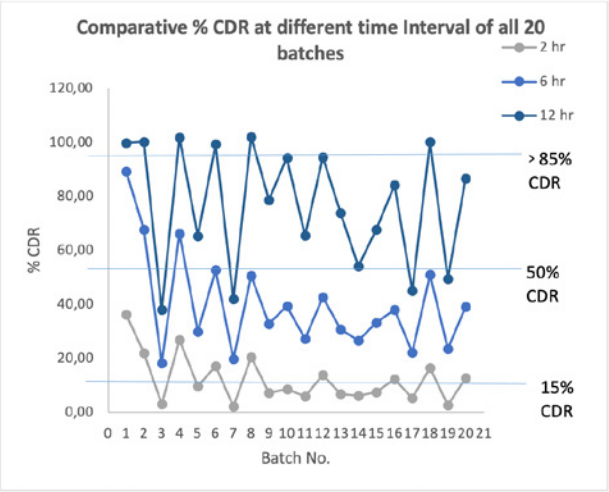

Figure 1. Comparative % Controlled drug release at different time Interval of all 20 batches (CDR: Controlled Drug Release)

The 3^2 full factorial design (X_1: concentration of sustained-release polymer; Kollidon SR, X_2: Concentration of hydrophilic polymer) with additional one categorical factor (X_3: Type of hydrophilic polymer; HPMC K4M or HPC) was constructed using Design expert® demo version 11 software (Stat-ease, MN, US). The 20 batches (18 design point batches with additional 2 replication of centre point for lack of fit test) (FSRT 1- FSRT 20) containing different compositions was suggested by the software. The design output with the level of actual factors and results for all responses are shown in table 3. Additionally, some measures of the influence on the response of single/individual components and in combination with other components were measured. The standard form of the quadratic equation was:

$$Quadratic: y = \sum_{i=1}^{q} b_i x_i + \sum \sum_{i<j}^{q} b_{ij} x_i x_{ij} \quad (1)$$

Where Y represents the response variable of the process.B*i*represents the coefficients of the factor's response to the pure blend X*i*=1and X*j*=0 when*j*≠*i*. The portion ∑*i*=1β*iXiis* called a linearblendingportion.Whenthereiscurvaturearisingfromnonlinearblendingbetweencomponentpairs, the parameters β*ij* represent either synergistic or antagonistic blending. Therapeutic values oftheregressioncoefficients-weredeterminedtoevaluatethesignificanceofthefactorsonthereresponses.ANOVAwasalsoappliedtodeterminethesignificanceof the model.

Model fitting and regression analysis

The experiments were performed in random order and it was observed that in all cases there exists a reasonable impact of independent variables. The results were fitted to different models and the residual errors were estimated to examine the goodness of fit for each model. The software suggests that

the best-fitted model was quadratic for Y_1 to Y_5. The model summary statistics are given in table 4. The regression coefficients for each of the responses were shown in table 5.

Table 4. Model summary statistics and Model selection

Responses	Models	SD	R^2	Adjusted R^2	Predicted R^2	PRESS	Observation
Y_1: % CDR 2hr	Linear	3.37	0.88	0.855	0.791	310.72	
	2FI	2.37	0.95	0.928	0.858	211.80	
	Quadratic	0.84	0.99	0.991	0.974	38.20	Suggested
	Cubic	0.32	1.00	0.999	0.992	12.38	Aliased
Y_2: % CDR 4hr	Linear	4.510	0.895	0.875	0.819	560.54	
	2FI	3.050	0.961	0.943	0.884	360.02	
	Quadratic	1.213	0.995	0.991	0.975	79.09	Suggested
	Cubic	0.454	1.000	0.999	0.996	11.61	Aliased
Y_3: % CDR 6hr	Linear	6.429	0.896	0.877	0.822	1133.54	
	2FI	4.551	0.958	0.938	0.876	789.56	
	Quadratic	1.831	0.994	0.990	0.975	159.84	Suggested
	Cubic	0.755	0.999	0.998	0.996	26.74	Aliased
Y_4: % CDR 8hr	Linear	5.663	0.947	0.937	0.913	843.68	
	2FI	5.057	0.966	0.950	0.906	911.56	
	Quadratic	4.620	0.976	0.958	0.896	1013.16	Suggested
	Cubic	3.657	0.992	0.974	0.814	1809.29	Aliased
Y_5: % CDR 12hr	Linear	7.186	0.913	0.897	0.858	1353.47	
	2FI	7.020	0.933	0.902	0.805	1851.68	
	Quadratic	6.260	0.955	0.922	0.809	1818.97	Suggested
	Cubic	2.321	0.997	0.989	0.960	380.68	Aliased

Model was selected based on Low PRESS value, Low SD, Highest R^2.Software have also suggested Aliased models too, which was omitted from selection criteria. CDR: Controlled Drug Release

Table 5. Regression analysis for Factorial design

Modelterm ▶	Model		Intercept	Maineffectterms			Twofactors Interactionterms			Square effect-Terms	
Response▼			X_1	X_2	X_3	X_1X_2	X_1X_3	X_2X_3	X_1^2	X_2^2	
Y_1: % CDR 2hr	Quadratic	FM	9.60	-2.94	9.12	3.20	-2.73	-1.22	1.61	0.62	3.53
		p-value	< 0.0001	*< 0.0001*	*< 0.0001*	*< 0.0001*	*< 0.0001*	*0.0004*	*< 0.0001*	*0.1357*	*< 0.0001*
		RM	9.91	-2.94	9.12	3.20	-2.73	-1.22	1.61	-	3.63
Y2: % CDR 4hr		FM	19.72	-5.53	13.36	3.66	-4.07	-1.65	1.81	1.07	4.37
		p-value	< 0.0001	< 0.0001	*< 0.0001*	*< 0.0001*	< 0.0001	*0.0006*	*0.0003*	*0.0435*	< 0.0001
Y3: % CDR 6hr		FM	34.95	-9.40	18.82	4.55	-5.94	-2.38	1.87	1.90	6.39
		p-value	< 0.0001	*< 0.0001*	*< 0.0001*	*< 0.0001*	*< 0.0001*	0.0009	0.0046	0.0469	*< 0.0001*
Y4: % CDR 8hr		FM	59.23	-11.28	24.38	5.34	-3.28	-1.35	-2.47	0.09	4.49
		p-value	< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.070	0.334	0.091	0.968	0.059
		RM	59.27	-11.28	24.38	5.34	-3.28	-	-2.47	-	4.51
Y5: % CDR 12hr		FM	80.81	-8.44	25.13	3.53	3.80	-0.76	-2.30	0.35	-6.66
		p-value	< 0.0001	0.001	< 0.0001	0.028	0.114	0.683	0.229	0.907	0.042
		RM	80.99	-8.44	25.13	3.53	3.795	-	-	-	-6.598

FM; Full model; RM: Reduced model
Term with p-value greater than 0.05 was omitted from full model
As per software suggestion, some insignificant terms were kept as it is required to maintain the hierarchy of model.

A positive value denotes an effect that favours the optimization, while a negative value indicates an inverse relationship between the factor and the response. The polynomial equation of the full model generated for each response is given below.

$Y1= 9.60C-2.94X_1+9.12X_2+3.20X_3-2.73X_1X_2-1.22X_1X_3+1.61X_2X_3+0.62X_1^2+3.53X_2^2$……..(2)

$Y2= 19.72C-5.53X_1+13.36X_2+3.66X_3-4.07X_1X_2-1.65X_1X_3+1.81X_2X_3+1.07X_1^2+4.37X_2^2$……..(3)

$Y3= 34.95C-9.40X_1+18.82X_2+4.55X_3-5.94X_1X_2-2.38X_1X_3+1.87X_2X_3+1.90X_1^2+6.39X_2^2$……..(4)

$Y4= 59.23C-11.28X_1+24.38X_2+5.34X_3-3.28X_1X_2-1.35X_1X_3+2.47X_2X_3+0.09X_1^2+4.49X_2^2$……..(5)

$Y5= 80.81C-8.44X_1+25.13X_2+3.53X_3+3.80X_1X_2-0.76X_1X_3-2.30X_2X_3+0.35X_1^2-6.66X_2^2$……(6)

The polynomial equation generated from the experimental design was validated by ANOVA and F statistics. ANOVA result and lack of fit tests of the models for all responses are shown in table 6.

Table 6. Model Testing Summary

	Source	SS	df	MS	F Value	p-value	R^2	Adj R^2	Pred R^2	F- Statistics
Y1:% CDR 2hr										
Regression	FM	1480.32	8.00	185.04	264.55	< 0.0001	0.995	0.991	0.974	F_{Cal}= 2.303 F_{Tab}= 4.844 DF = (1, 11) α =0.05
	RM	1478.51	7.00	211.22	266.62	< 0.0001	0.994	0.990	0.974	
Residual	FM	7.69	11	0.70						
	RM	9.51	12	0.79						
	LackofFit	9.35	10	0.93	11.65	0.082				
	Pure Error	0.16	2	0.08						
Y2: % CDR 4hr										
Regression	FM	3085.885	8	385.74	262.26	< 0.0001	0.995	0.991	0.975	No need-mod-elreduction
Residual	FM	16.179	11	1.471						
	LackofFit	15.404	9	1.712	4.4142	0.19830				
	Pure Error	0.775	2	0.388						
Y3: % CDR 6hr										
Regression	FM	6347.21	8	793.40	236.73	< 0.0001	0.994	0.990	0.975	No need-mod-elreduction
Residual	FM	36.87	11	3.352						
	LackofFit	34.242	9	3.80	2.90	0.283				
	Pure Error	2.625	2	1.31						
Y4: % CDR 8hr										
Regression	FM	9509.56	8	1188.70	55.69	< 0.0001	0.976	0.958	0.896	F_{Cal}= 0.512 F_{Tab}= 3.982 DF = (2,11) α =0.05
	RM	9487.71	6	1581.29	80.10	< 0.0001	0.974	0.962	0.930	
Residual	FM	234.777	11	21.343						
	RM	256.628	13	19.741						
	LackofFit	249.283	11	22.662	6.17	0.148				
	Pure Error	7.345	2	3.673						
Y5: % CDR 12hr										

	Source	SS	df	MS	F Value	p-value	R^2	Adj R^2	Pred R^2	F- Statistics
Regression	FM	9079.32	8	1134.92	28.96	< 0.0001	0.955	0.922	0.809	F_{Cal}= 0.604
	RM	9008.27	5	1801.65	50.23	< 0.0001	0.947	0.928	0.879	F_{Tab}= 3.587
Residual	FM	431.06	11	39.19						DF = (3,11)
	RM	502.11	14	35.865						α =0.05
	LackofFit	487.639	12	40.64	5.62	0.161				
	Pure Error	14.472	2	7.24						

SS: sum of squares; df: Degree soffreedom; MS: mean of squares; F: Fischer's ratio; R2: Regression coefficient; FM: Full model; RM: Reduced model; FTab: Table value of F; FCal: calculated value of F. Details of calculations are shown by MendenhallWandSincich. If F_{Tab} is greater than the F_{Cal} that indicating the reduced term does not contribute significantly to the prediction of responses and therefore can be omitted from the full model and reduced model can be used for optimization prediction.

It has indicated significant effects of the independent factors (P > F) on response Y_1 to Y_5. The larger F-value recommends that the data fit to the model were significant and leads to a good correlation with a high R^2 value. For all responses, adjusted and predicted R^2 values were in reasonable agreement, demonstrating the mathematical model describes the data adequately. However, certain model terms for Y_1, Y_4, and Y_5 having P>0.05 require a model reduction to improve the model. Removal of this insignificant term improved the model for Y_1, Y_4, and Y_5 responses. The polynomial equation of the reduced model was generated for each response as given below.

$$Y1= 9.91C-2.94X_1+9.12X_2+3.20X_3-2.73X_1X_2-1.22X_1X_3+1.61X_2X_3+3.53X_2^2 \quad (7)$$

$$Y2= 19.72C-5.53X_1+13.36X_2+3.66X_3-4.07X_1X_2-1.65X_1X_3+1.81X_2X_3+1.07X_1^2+4.37X_2^2 \quad (8)$$

$$Y3= 34.95C-9.40X_1+18.82X_2+4.55X_3-5.94X_1X_2-2.38X_1X_3+1.87X_2X_3+1.90X_1^2+6.39X_2^2 \quad (9)$$

$$Y4= 59.27C-11.28X_1+24.38X_2+5.34X_3-3.28X_1X_2-2.47X_2X_3+4.51X_2^2 \quad (10)$$

$$Y5= 80.99C-8.44X_1+25.13X_2+3.53X_3+3.80X_1X_2-6.66X_2^2 \quad (11)$$

The F statistics was used to test the generated reduced model, shows that the F_{Tab} was greater than the F_{Cal} for all the responses indicating for the reduced term which does not contribute significantly to the prediction of responses and therefore can be omitted from the full model (Table 6). An insignificant lack of fit for all responses also implies that the models were adequate for the prediction with the range of experimental variables.

Direct interpretation of reduced polynomial equations may lead to errors since interaction and polynomial terms are also significant. Therefore, contour and response surface plots were drawn. Nonlinear relationship is visible in all contour and 3D surface plots (Figure 2).

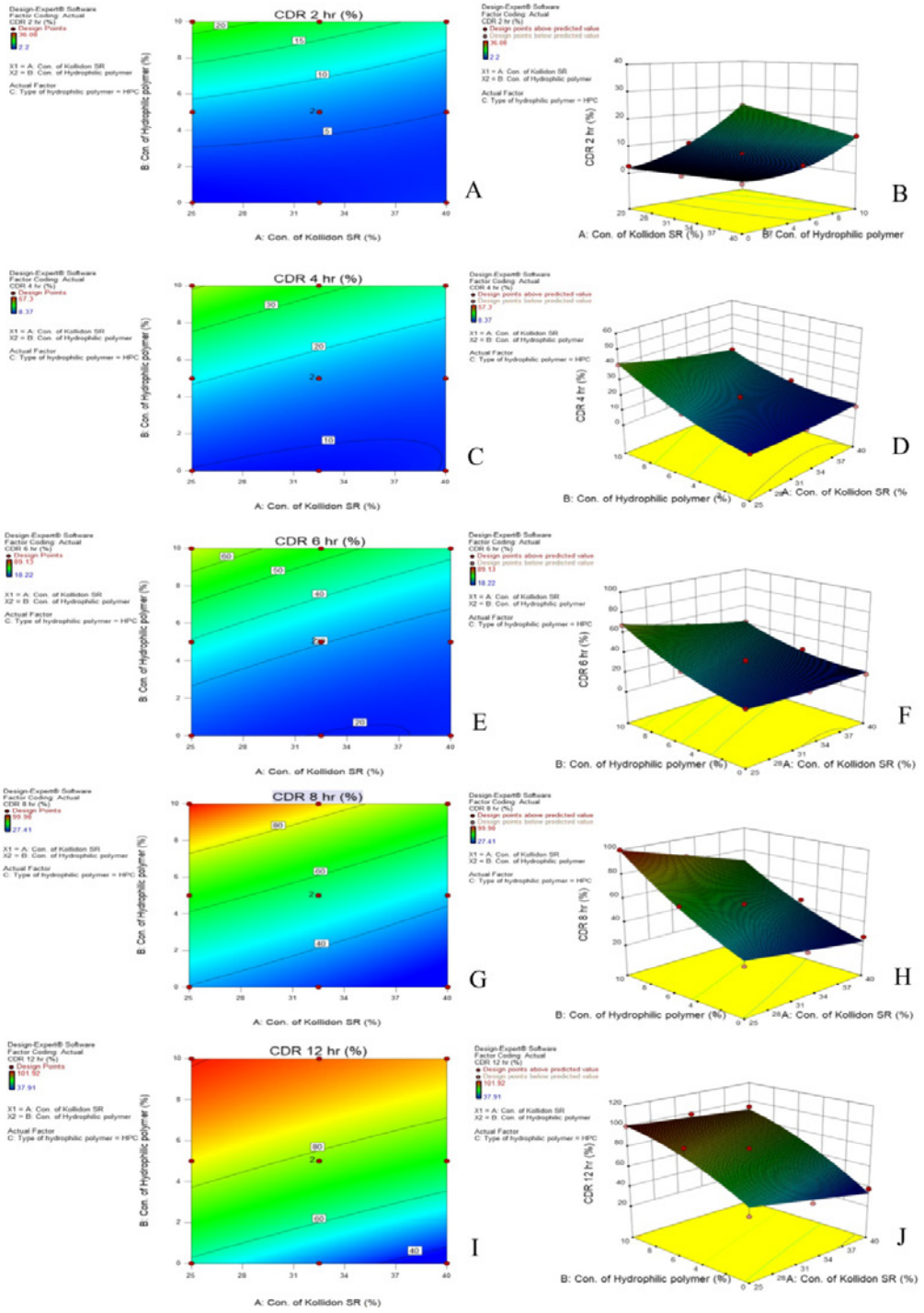

Figure 2. Contour Plots and 3D surface plots for Responses [For Y1 (A, B), Y2 (C, D), Y3 (E, F), Y4 (G, H) and Y5 (I,J)]

Design space can be identified based on the highest and the lowest range of variables set by the user. These plots help to constitute desired responses and formulation compositions. In the two-dimensional view of the contour plots, constant responses are connected to construct the contour line. On the other hand, a 3D view of the surface plot may serve a clearer picture of the response surface.After generating the reduced model polynomial equations to relate the dependent and independent variables, the formulation was optimized using all five responses. The formulation was optimized based on the constraints set on the independent variable as shown in table 7.

Table 7. Target responses for selection of optimum formulation

Response Variables	Range	Target	TI Low	TI High
Y1: % CDR 2hr	10-20	15	13.24	17.79
Y2: % CDR 4hr	21-30	25	22.95	29.25
Y3: % CDR 6hr	31-50	40	37.11	46.61
Y4: % CDR 8hr	51-75	62.5	63.54	71.34
Y5: % CDR 12hr	NLT 85	>85	86.18	96.1
CDR: Controlled Drug Release ;TI: Tolerance interval				

The optimized composition of febuxostat sustained-release tablet [FSRT-OB; Concentration of Kollidon SR (X_1) = 38.50 %w/w, Concentration of hydrophilic polymer (X_2) = 7.72 %w/w, Type of hydrophilic polymer (X_3) = HPMC K4M] was used for formulation development and it was evaluated for physical and chemical characteristics[18].The composition of optimized batch (FSRT-OB) is shown in table 8. Checkpoint validation results suggest that there was reasonable agreement between predicted and experimental (percentage bias < 10%) in all responses. So, the model can be said to be valid for the given factorial design[19].The optimized powder blend was prepared by mixing all ingredients in a polythene bag. The prepared powder blend of optimized batch (FSRT-OB) was compressed using direct compression method and evaluated for physical and chemical characteristics (Angle of repose, Compressibility index, Hausner's ratio, Hardness Friability, Weight variation, and Assay)[20].All results were within acceptance criteria.

Table 8. Composition for optimized batch (FSRT-OB)

Ingredients	Qty	Qty/Tab
Febuxostat solid dispersion (FSD24) equivalent to 40mg of febuxostat	120 mg	120
Avicel PH 102	QS	11.95
Kollidon SR (X_1)	38.50 %w/w	96.25
HPMC K4M (X_2, X_3)	7.72%w/w	19.3
Silicon dioxide	0.5 %w/w	1.25
Magnesium stearate	0.5%w/w	1.25
Total Weight each Tablet	250 mg	
Desirability	1	
HPMC K4M; Hydroxypropyl methylcellulose K4M		

Conclusion

The successful improvement in the rate of dissolution of febuxostat was obtained by preparing amorphous solid dispersion with Kollidon SR (38.50%w/w) and HPMC K4M (7.72%) using the spray drying technique. In all the prepared batches, it was clear that the solubility of the drug was sustained in the case of sustained-release tablets prepared with HPMC K4M as compared to HPC. Product properties including solubility, dissolution rate, and amorphous characteristics were improved by applying full

factorial design and results showed good agreement with the prediction of the models. From the evaluation parameters of all batches, it can be concluded that the Kollidon SR provided a sustained release to the tablets. It can be concluded that the optimization provides help in selecting the appropriate number of dependent variables to achieve the required goal.

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