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Research Article

Febuxostat Loaded Microballoons: A Novel Approach for Gastric Retention

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ABSTRACT

Febuxostat loaded microballoons (FEB-MBs) were formulated using a non-aqueous solvent evaporation method using Eudragit RS 100, HPMC K4 M as a polymer, and span 80 as a surfactant. The ratio of solvents like methanol and dichloromethane, liquid paraffin as a processing medium. The formulation was optimized by the Box-Behnken design. Optimized formulation was evaluated for particle size, entrapment efficiency, % buoyancy, Percentage yield, *in-vitro* release studies, and stability study. Mean particle size 80.11 ± 0.349, entrapment efficient 83.25 ± 0.526, and % buoyancy 92.41 ± 0.57 were found for optimized formulation. Scanning electron microscopy (SEM) image of formulation shows discrete particle size with smooth surface texture with a hollow space and spherical shape and particle size < 200 µm. The result of *in-vitro* study shows an improved rate of drug release for a longer period from FEB-MBs compared with pure drugs. This is due to increases in the surface area leads to increases in absorption. The stability study shows no significant change in microballoons of the optimized formulation after 30 days of storage as per ICH guidelines. This multi particulate system provides an excellent approach for sustained release of a medicament for longer, thereby reducing dose frequency.

Introduction

Microballoons are gastro retentive drug-delivery systems with a non-effervescent approach. Micro balloons (Hollow microsphere) are empty particles of spherical shape without core in the strict sense. These microspheres are characteristically free-flowing powders comprising proteins or synthetic polymers, ideally having a size of less than 200 µm.

Gastro-retentive Microballoons are low-density systems with sufficient buoyancy to float over gastric contents and remain in the stomach for a prolonged period. The drug is released slowly at the desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. The drugs having short half-life can be formulated as Microballoons for better therapeutic effect, furthermore, it reducing dosing frequency, thereby improving patient compliance. Enhanced absorption of drugs that solubilize only in the stomach. Gastric retention time is increased because of buoyancy. Microballoons are considered one of the most favorable buoyant systems with the unique advantages of multiple unit systems and better-floating properties because of the central hollow space inside the microsphere.[1]

When microballoons contact gastric fluid, the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microballoons. However, a minimal

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gastric content is needed to allow proper achievement of buoyancy.[2]

Febuxostat is a non-purine selective inhibitor of xanthine oxidase. Hence, Febuxostat inhibits xanthine oxidase and therefore reduces the production of uric acid, excess of which is responsible for the gout disease. Febuxostat is not recommended for the treatment of asymptomatic hyperuricemia. Its bioavailability is about 49%[3,4] and the biological half-life is about 5-8 hours. It is the physical properties of non-hygroscopic and white crystalline powder. This drug-protein binding is about 99%, and the volume of distribution is about 50 L. The route of elimination of Febuxostat is primarily through both hepatic and renal pathways. The recommended dose is 40 mg, 80 mg, and 120 mg once daily. It comes as a tablet to take by mouth with or without food. The common side effects of febuxostat are Arm, back, or jaw pain, Bloody nose, Chest pain or discomfort, Cloudy urine, decreased frequency or amount of urine, Diarrhea, Difficult or labored breathing.[5-7]

Gout is a rheumatic inflammatory condition that develops in some people who have a high uric acid level in their blood. The acid converted to the needle-like crystal in some joints and bonds and caused sudden and severe episodes of pain, tenderness, redness, warmth, and swelling. Risk factors for the increase in uric acid include nutritional, hematological, and genetic factors. Other miscellaneous factors, such as obesity and excessive alcohol consumption, also increase urate production in the body.[8,9]

The present research work aims to develop febuxostat-loaded microballoons for the effective treatment of gout. Febuxostat belongs to BCS class II, which is having low solubility and high permeability. Due to short residence time in upper GIT, effective concentrations cannot be achieved and thus fluctuation in plasma drug concentration occurs, leading to failure of therapeutic intervention. Poor oral bioavailability leads to reduction in plasma drug concentration and overall reduction in therapeutic effect. The reason behind formulating febuxostat loaded microballoons is improvement in gastric retention time which facilitate maximum time for drug in gastric environment which leads to increases the rate of dissolution and thereby increases the absorption. It will also avoid gastric irritation due to a sustained release effect. As compare to single unit dosage form multi-unit drug delivery facilitate maximum surface area for drug absorption.

Materials and Methods

Materials

Febuxostat was obtained as a gift sample (API) from Zydus Cadila Healthcare, Ahmedabad, India. Polymer like Eudragit RS 100, Eudragit RL 100, HPMC, HPMC K4 M, Ethyl Cellulose, Chitosan from ChemDyes Corporation. Solvents like Methanol, Dichloromethane, Chloroform, Diethyl ether, Toluene, Acetone, Petroleum ether from ChemDyes Corporation. Surfactant like Tween 80 and Span 80 from ChemDyes corporation. Liquid paraffin heavy as a processing medium from ChemDyes corporation.

Methods

Solubility of Drug in Different Solvents

Solubility of drugs in different solvents was done by quantitative method. The drug was dissolved in 10 mL of solvents with increments of 1 mg until it reached saturation. The point at which the drug fails to dissolve is noted down.[10]

Drug Identification and Compatibility of Drug and Excipients by FT-IR

The identification of drugs and interaction between drugs and excipients can be identified by Fourier transform infrared spectroscopy. Potassium bromide was mixed with the sample to be analyzed in the weight ratio of 100:1 (KBr:Drug), and the pellet was prepared using KBr pellet press, and spectrum was taken using FTIR. FTIR spectrum of Febuxostat was compared with spectrum of mixture of Febuxostat + Eudragit RS 100 + HPMC K4 M + Span 80. Disappearance of Febuxostat peak or shifting of peak in any of the spectra was studied.

Selection of Excipients

Solubility of Polymers in Different Solvents

Solubility of various polymers in different solvents was done by quantitative method. The solubility determination of polymers in various solvents was performed by adding polymers in increments of 1 mg until it failed to dissolve further in the fixed 1 mL of solvent. After polymers soluble or insoluble in solvents were determined.[10]

Formulation and Development

Method of preparation of Febuxostat Loaded Microballoons by Non-aqueous Solvent Evaporation Method

Accurately weighed amount of drug and polymer and after drug was added to the polymer which was dissolved in the mixture of solvent ratio 1:1 (methanol and dichloromethane) to get the organic phase. Liquid paraffin was taken in another beaker and a different concentration of Span 80 as a surfactant was added to get the oily phase. The oil phase was placed under constant stirring on a mechanical stirrer at different RPM speeds and maintained 40°Ċ temperature to which the organic phase was added drop by drop. The stirring was continued for 4 hours until the organic solvents were evaporated completely to yield microballoons. The obtained microballoons were filtered and washed with petroleum ether to remove paraffin and then dried at room temperature.[11]

Optimization of the Formulation Parameters

In order to obtain optimized formulation using a minimum number of trial runs, the Box-Behnken design was used. Stat-Ease Design-Expert v7.0.0 was used for optimization. A complete Box-Behnken design was utilized to study the effect of independent variables on the dependent variables in the formulation of microballoons. Independent variables were selected for the study is the concentration of Eudragit RS 100 (X1), the concentration of HPMC K4 M (X2), the emulsifier concentration (X3), and Stirring speed (X4). Each independent factor has three levels, High, Medium and low. Dependent variables were Particle size (Y1), % Entrapment Efficiency (%EE) (Y2) and % Buoyancy (Y3). Values and responses of both independent and dependent variables are listed in Table 1 and composition of Microballoons Formulation show in Table 2.

Table 1: Optimization factors with levels

Factors	*Levels*		
Independent Variables	Low (-1)	Medium (0)	High (+1)
X1 Concentration of Eudragit RS 100 (mg)	100	300	500
X2 Concentration of HPMC K4 M (mg)	100	300	500
X3 Emulsifier concentration (%)	0.50	0.75	1.00
X4 Stirring speed (RPM)	300	500	700
Dependent Variables	*Response*		
Y1	Particle size (μm)		
Y2	% Entrapment efficiency		
Y3	% Buoyancy		

Interaction Between the Factors

The statistical evaluation of all the obtained data was carried out by analyzing variance (ANOVA) using DOE software. The results of ANOVA (P-value) showed the effect of various independent variables on the particle size, %EE and % buoyancy. After regression analysis of all the formulations, the full polynomial model was obtained, followed by the omission of non-significant terms ($p > 0.05$) to obtain a reduced analysis model. This equation represents the effects of independent variables on the dependent variables.

Table 2: Composition of Microballoons Formulation

		Independent Variables			
Batch No.	*Drug (mg)*	*Concentration of Eudragit RS 100 (mg) (X1)*	*Concentration of HPMC K4 M (mg) (X2)*	*Concentration of surfactant (%) (X3)*	*Stirring speed (RPM) (X4)*
MB 1	100	100	100	0.75	500
MB 2	100	100	300	0.75	300
MB 3	100	500	100	0.75	500
MB 4	100	500	300	0.75	700
MB 5	100	300	500	1	500
MB 6	100	300	100	0.75	700
MB 7	100	300	300	1	300
MB 8	100	100	500	0.75	500
MB 9	100	100	300	0.5	500
MB 10	100	300	500	0.5	500
MB 11	100	300	300	0.5	300
MB 12	100	100	300	1	500
MB 13	100	500	300	0.5	500
MB 14	100	300	500	0.75	300
MB 15	100	300	500	0.75	700
MB 16	100	500	300	1	500
MB 17	100	300	300	0.5	700
MB 18	100	300	100	1	500
MB 19	100	300	300	1	700
MB 20	100	500	500	0.75	500
MB 21	100	100	300	0.75	700
MB 22	100	300	300	0.75	500
MB 23	100	300	100	0.75	300
MB 24	100	500	300	0.75	300
MB 25	100	300	100	0.5	500

Preparation of Optimized Formulation Based on the Desirability Function

Optimization was carried out to ascertain the level of independent variables (X1, X2, X3, and X4) that would provide data of Y1, Y2, and Y3. When developing the formulation, the response has been united to design the product of the required attribute. The main function of the desirability was to join every response in a single experiment and provide the probability of predicting the highest level for independent variables. The last optimized formulation, suggested by the software, was prepared, and parameters were compared to the expected value given by the software.

Evaluation of Febuxostat Loaded Microballoons

Particle Size

The particle size of the microballoons was measured with a digital microscope equipped with a camera, and the mean microballoons size was determined by measuring 100 particles with a digital microscope.[12]

Percentage Yield

The percentage yield of floating microballoons was determined by dividing the product's actual weight by the total value of all non-volatile components used to prepare floating microballoons, as represented by the formula below.[12,13]

$$\%\ Yield = \frac{\text{Actual weight of product}}{\text{Total weight of drug and excipients}} \text{ X } 100$$

Drug Entrapment Efficiency

Microballoons, equivalent to 10 mg drug, was crushed in a glass mortar. Volume was then made up to 10 mL with methanol in a volumetric flask. The solution was dissolved after then filtered, and absorbance was noted at 315 nm. The amount of drug entrapped in the microballoons was calculated using the following formula:

$$\%\ \text{Entrapment Efficiency} = \frac{\text{Calculated Drug Concentration}}{\text{Theoretical Drug Concentration}} \text{ X } 100$$

In-vitro Buoyancy

The microballoons (100 mg) spread over 900 mL of 0.1 N HCl containing 0.02% Tween 80 as a surfactant, the floating behavior of microballoons was examined using a USP dissolution test apparatus II. The medium was held at 37°C and agitated with a paddle that rotated at 100 rpm. The floating and settling parts of the microballoons were divided after 12 hours. The separated parts were filtered and dried. The percentage of floating microballoons were calculated using following formula.[12,13]

$$\%\ Buoyancy = \frac{Weight\ of\ floating\ Microballons}{Initial\ Weight\ of\ Floating\ Microballoons} X100$$

In-vitro Drug Release Study

In a USP dissolution test apparatus II paddle-type dissolution assembly, *In vitro* dissolution experiments are possible. Microballoons containing the medication dose are applied to 900 mL of 0.1 N HCl containing 0.02% Tween 80 (surfactant) as a dissolution medium, with the stirring speed set to 100 rpm at 37 ± 0.5°C. Samples are collected at regular intervals and analyzed at 321 nm using any appropriate analytical process, such as UV visible spectroscopy. [12, 13]

Characterization of Optimize Microballoons

FT-IR Study of Microballoons

It is necessary to identify the interaction that may occur during the manufacturing process of the microballoons. The IR spectrum of formulated microballoons was measured by FT-IR spectrometer. In this process, a sample of microballoons was mixed with KBr, compressed to form a thin pellet, and then used for testing. The recording range for the measurement was 4000–400 cm^{-1}. [12,13]

Scanning Electron Microscopy (SEM)

The external and internal morphology of the microballoons is examined using scanning electron microscopy (SEM). The SEM samples were produced by gently sprinkling microballoons powder on a double adhesive tape applied to a stub. The stubs were then coated with platinum in an argon atmosphere using a gold sputter module in a high vacuum evaporator. The samples were then randomly scanned, and photomicrographs with higher magnification were taken for surface morphology.[14]

Stability Study

The optimized formulation was sealed in aluminum packaging that was polyethylene-coated on the inside. For three months, the samples were kept in a stability chamber (Frontline electronic and machinery Pvt. Ltd) at 40°C and 75% RH (Relative humidity). After the studies, samples were examined for physical appearance and drug entrapment efficiency.

Result and Discussion

Solubility of Drug in Different Solvents

The solubility study of Febuxostat was done by quantitative method. The amount of drug dissolved in a solvent like methanol, dichloromethane, acetone, chloroform, diethyl ether, and toluene was determined. Febuxostat has the highest solubility in acetone compared with methanol, although for the calibration curve of febuxostat methanol is used as a solvent. Because acetone having cut off wavelength at 330 nm. Cut-off wavelength may be defined as a region where the solvent absorbs the UV or Visible light. At this wavelength, measurement must be avoided because it is difficult to determine the absorbance comes from the solvent or your solute. The λ_{max} of Febuxostat is 315 nm so it is better to use methanol instead of using acetone for a calibration curve.

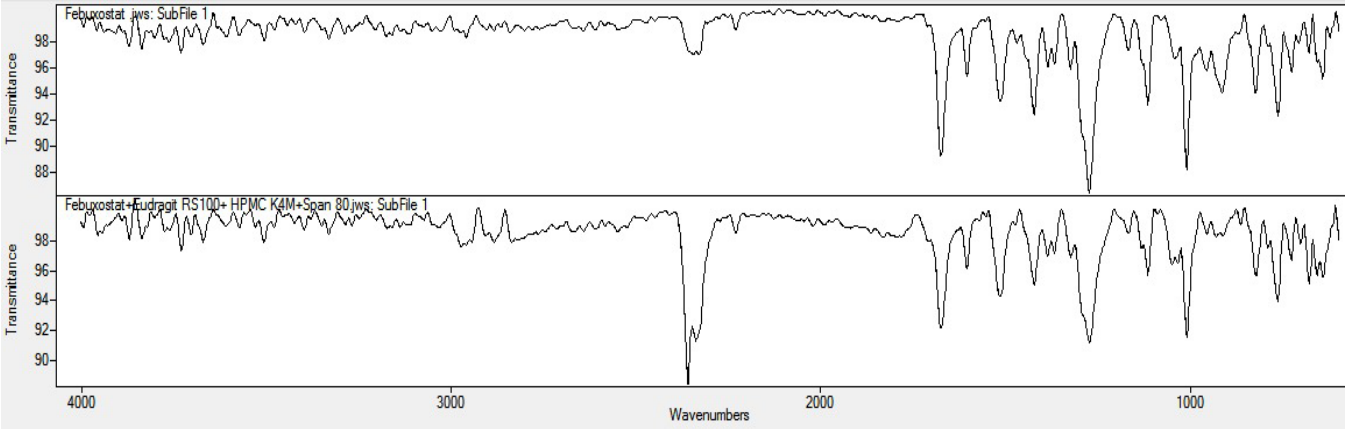

Fig. 1: FT-IR Spectrum of drug and excipients

Table 3: FT-IR data of drug and excipient

	Wave number(cm^{-1})		
Group	*Standard peak of pure Febuxostat drug*	*Febuxostat API*	*Febuxostat + Eudragit RS 100 + HPMC K4 M + Span 80*
O – H Stretching	3300 – 2500	2958.36	2958.32
C = N Stretching	2259	2328.75	2338.07
COOH Group	1694	1675.5	1675.07
C = C Stretching	1608 – 1513	1604.5	1604.52

Drug Identification and Compatibility of Drug and Excipients by FT-IR

FT-IR spectrum of Febuxostat, Febuxostat + Eudragit RS100 + HPMC K4 M + Span 80. From the spectrum (Fig. 1 and Table 3), it can be concluded that there was no major changes observed in the peak of the drug and drug + excipient mixture when compared with the standard peak.

Selection of Excipients

Solubility of various polymers in different solvents was done by quantitative method. The amount of polymers like Eudragit RS 100, Eudragit RL 100, HPMC, HPMC K4 M, Ethyl Cellulose, Chitosan dissolved in Solvents like Methanol, Dichloromethane, Chloroform, Petroleum ether. Results it can be concluded that polymer like HPMC K4 M and Eudragit RS 100 is soluble in methanol and dichloromethane. Then other polymers are sparingly soluble and insoluble in all the solvents. As discussed earlier, the drug Febuxostat is freely soluble in methanol and dichloromethane. After that, selecting polymers is Eudragit RS 100, HPMC K4 M, and selecting solvents is methanol and dichloromethane.

Formulation and Development

Optimization af Formulation Parameters

After optimization of formulation parameter based on Particle size, %EE and %buoyancy, response surface method (box-Behnken design) applied by design expert software 7. The Concentration of Eudragit RS 100 (X1), the concentration of HPMC K4 M (X2), the concentration of surfactant (X3), and Stirring speed (X4) taken as an independent variable at three levels low (-1), medium (0) and high (+1). Particle size (Y1), %EE (Y2), and %buoyancy (Y3) were taken as dependent variables. Table 4 shows that Particle size varies from 19.31 ± 2.298 µm to 109.13 ± 2.597 µm and %EE varies from 60.69 ± 2.105 % to 95.67 ± 2.058 % and %buoyancy varies from 61.23 ± 0.806 % to 95.43 ± 0.724 % .

With the help of ANOVA and constructing polynomial equation, variation in the particle size, %EE, and % buoyancy were evaluated.

$$Y1 \text{ (Particle Size)} = + 61.63 + 15.22 *X1 + 5.41 *X2 - 0.13 *X3 - 24.46 *X4$$

$$Y2 (\%EE) = + 73.50 + 6.83 *X1 + 2.53 *X2 - 0.31 *X3 - 11.10 *X4$$

$$Y3 (\% \text{ Buoyancy}) = + 79.28 - 3.65 *X1 - 2.52 *X2 - 12.37 *X3 + 0.24 *X4$$

The F-value for particle size was 12.70, for %EE 12.86 and for %buoyancy 341.76 which indicate the model is significant. There is only a 0.01% chance that a "Model F-value" this large could occur due to noise.

Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case, particle size, %EE of X1, X4, and % buoyancy of X1, X2, X3 are significant model terms. Values greater than 0.1000 indicate that the model terms are not significant. If there are many insignificant

Table 4: Optimization of formulation parameter

	Dependent variables		
Batch No.	*Particle size (μm) (Y1)*	*Entrapment efficiency (%) (Y2)*	*In vitro buoyancy (%) (Y3)*
MB 1	35.02 ± 0.746	61.87 ± 1.905	85.23 ± 1.339
MB 2	54.088 ± 1.126	71.18 ± 1.545	84.37 ± 0.894
MB 3	32.59 ± 1.719	60.69 ± 2.105	79.42 ± 1.064
MB 4	66.96 ± 2.306	75.02 ± 1.021	77.81 ± 1.01
MB 5	59.006 ± 1.647	73.21 ± 1.434	63.45 ± 0.618
MB 6	19.31 ± 2.298	54.84 ± 1.083	82.51 ± 0.806
MB 7	109.13 ± 2.597	95.67 ± 2.058	65.76 ± 0.946
MB 8	46.28 ± 1.325	66.37 ± 1.414	80.81 ± 1.538
MB 9	60.1 ± 2.506	73.45 ± 2.046	95.43 ± 0.724
MB 10	55.86 ± 2.646	71.78 ± 2.201	88.23 ± 0.325
MB 11	90.6 ± 2.808	87.52 ± 0.797	90.34 ± 0.606
MB 12	46.8 ± 1.405	66.59 ± 1.667	70.36 ± 1.381
MB 13	93.63 ± 1.954	89.47 ± 0.75	87.12 ± 1.169
MB 14	89.59 ± 0.838	84.26 ± 1.604	77.09 ± 0.489
MB 15	44.79 ± 2.076	64.95 ± 2.05	76.14 ± 0.99
MB 16	89.77 ± 0.675	85.31 ± 2.328	61.23 ± 0.806
MB 17	45.03 ± 1.641	64.73 ± 0.835	90.67 ± 0.704
MB 18	61.11 ± 0.96	74.01 ± 0.987	68.61 ± 1.355
MB 19	38.12 ± 0.835	62.01 ± 1.207	67.12 ± 1.176
MB 20	65.46 ± 1.596	75.05 ± 1.239	75.27 ± 0.71
MB 21	25.48 ± 1.459	57.67 ± 0.914	84.71 ± 1.002
MB 22	62.06 ± 1.534	74.62 ± 0.99	78.54 ± 0.852
MB 23	87.81 ± 1.931	80.24 ± 0.733	82.23 ± 0.783
MB 24	101.95 ± 1.234	93.52 ± 1.061	76.29 ± 0.818
MB 25	60.25 ± 0.828	73.59 ± 0.855	93.17 ± 0.285

Mean ± SD, n = 3

model terms (not counting those required to support hierarchy), model reduction may improve your model.

Influence of Concentration of Eudragit RS 100 and Concentration of HPMC K4 M on the Particle Size

The concentration of Eudragit RS 100 shows a positive influence on particle size. An increase in the concentration of Eudragit RS 100 will significantly increase particle size. The concentration of HPMC K4 M positively affects the particle size as the concentration of HPMC K4 M increases improvement in the particle size was observed. Moreover, the role of concentration of surfactant and stirring speed of increase then particle size decrease and concentration of surfactant and stirring speed of decrease then particle size increase show the formulation. 3D surface plot and countor plot are shown in Fig. 2.

Influence of Concentration of Eudragit RS 100 and Concentration of HPMC K4 M on the %EE

The concentration of Eudragit RS 100 shows a positive influence on %EE. An increase in the concentration of Eudragit RS 100 will significantly increase %EE. The concentration of HPMC K4 M positively affects the %EE as the concentration of HPMC K4 M increases improvement in the %EE was observed. 3D surface plot and countor plot are shown in Fig. 3.

Influence of Concentration of Eudragit RS 100 and Concentration of HPMC K4 M on the %buoyancy

The concentration of Eudragit RS 100 shows negative influence on %buoyancy. An increase in the concentration of Eudragit RS 100 will significantly decrease % buoyancy. The concentration of HPMC K4 M negatively affects the %buoyancy as the concentration of HPMC K4 M increases, then decreases in the %buoyancy was observed. The formulation shows the role of surfactant concentration increase then %buoyancy decrease and concentration of surfactant decrease then %buoyancy increase. 3D surface plot and countor plot are shown in Fig. 4.

Preparation of Optimized Batch Based on Desirability Function

During formulation optimization, all responses were considered to find the desirability characteristic of the formulation. The desirability function combines all the responses into one variable to predict the optimal levels

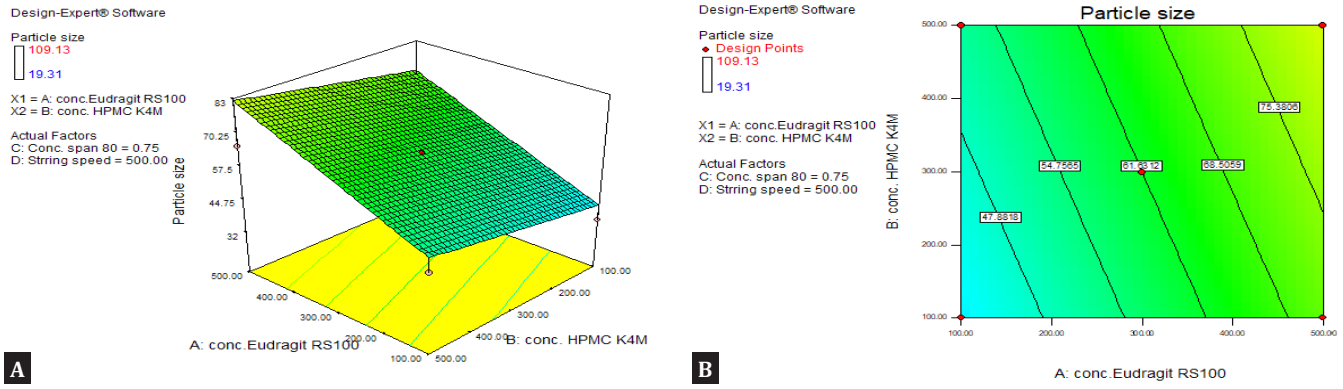

Fig. 2: (A) 3D Response surface plot for particle size; (B) Contour Plot for Particle Size

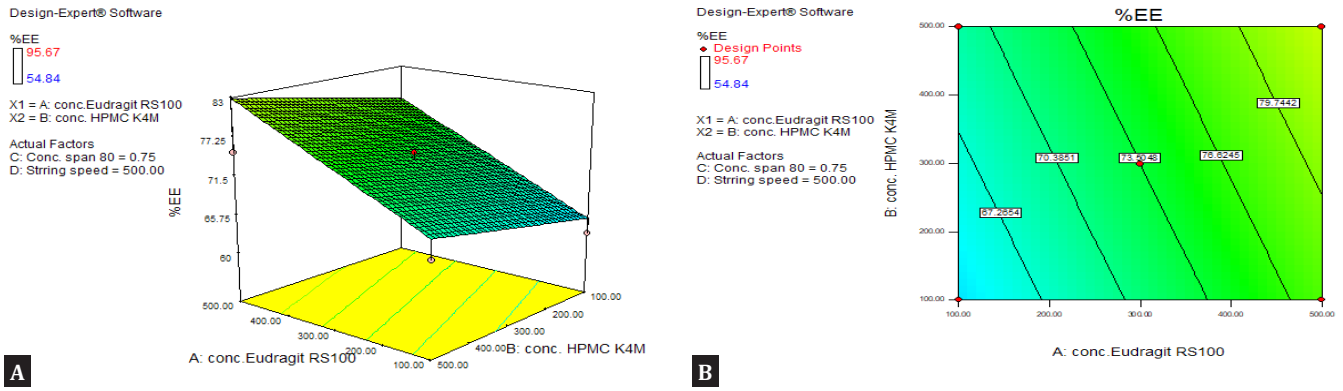

Fig. 3: (A) 3D Response surface plot for %EE; (B) Contour plot for %EE

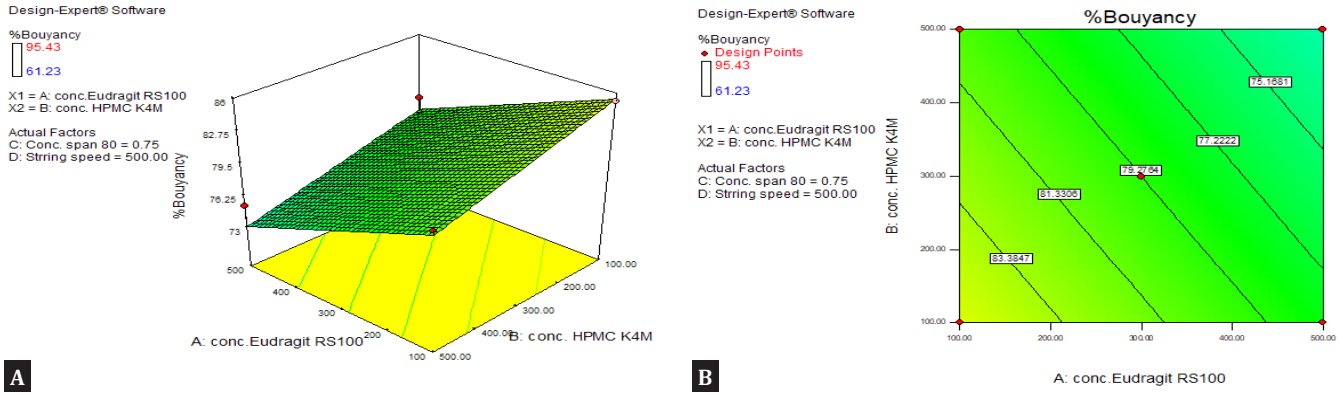

Fig. 4: (A) 3D Response surface plot for % buoyancy; (B) Contour plot for %Buoyancy

Table 5: Formulation of Optimized Batch

Batch No.	*Drug (mg)*	*Concentration of Eudragit RS 100 (mg)*	*Concentration of HPMC K4 M (mg)*	*Concentration of surfactant (%)*	*Stirring speed (RPM)*	*Desirability*
MB 28	100	488.96	100.01	0.50	385	0.710

for the independent variables. The desirability value of 0 represents an unacceptable response, and 1 represents the response's most significant and desired value. The response of the box-behnken design formulation shown in Table 5 suggested concentration Eudragit RS 100: 488.96 mg, concentration of HPMC K4 M: 100.01 mg, concentration of surfactant: 0.50%, and stirring speed: 385 RPM with 0.710 desirabilities.

Evaluation of Optimized Batch of Microballoons

Particle size, %EE and %Buoyancy

An optimized batch of Particle size value was found to be 80.11 ± 0.349 µm and %EE of the optimized batch was 83.25 ± 0.526%, and %Buoyancy of optimized batch was 92.41 ± 0.57%, which is nearer to predicted value that given by software shown in Table 6. So from the data it can be concluded that the model developed by the software

Table 6: Results of Particle Size, %EE and %Buoyancy of optimized batch

	Experimental Value			*Predicted Value*		
Optimized batch	*Particle size (µm)*	*% EE*	*% Buoyancy*	*Particle size (µm)*	*% EE*	*% Buoyancy*
MB 28	80.11 ± 0.349	83.25 ± 0.526	92.41 ± 0.57	84.67	84.06	90.57

(Mean±SD, n=3)

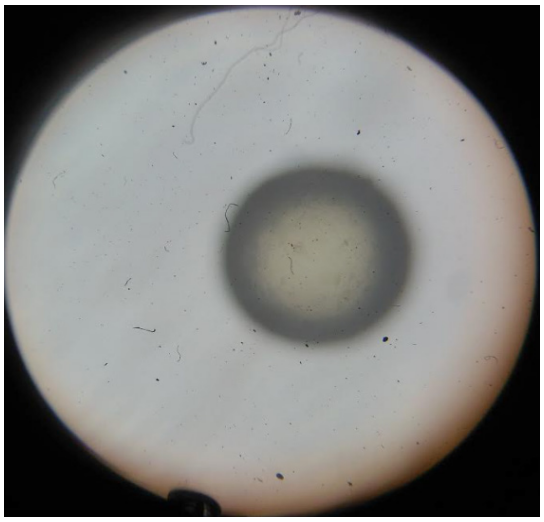

Fig. 5: Microscope image

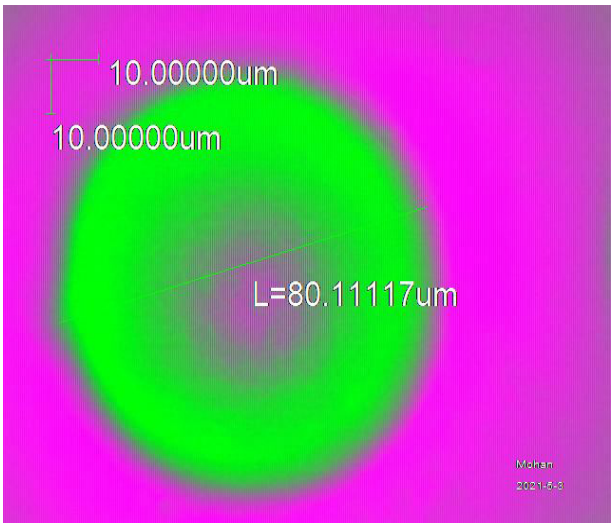

Fig. 6: Digital microscope image

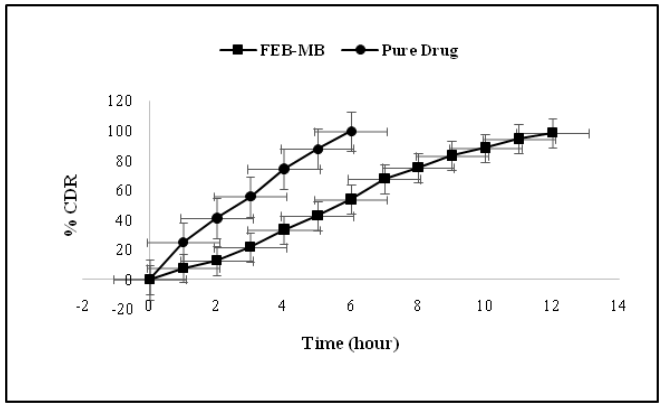

Fig. 7: Graphical representation of *In-Vitro* drug release study

Table 7: Comparison of FT-IR spectrum of pure drug and ebuxostat loaded microballoons

	Wave number (cm^{-1})	
Group	*Pure Febuxostat drug*	*Febuxostat Loaded Microballoons*
O – H Stretching	3231	3232.11
C = N Stretching	2840.63	2846.42
COOH Group	1686.44	1728.87

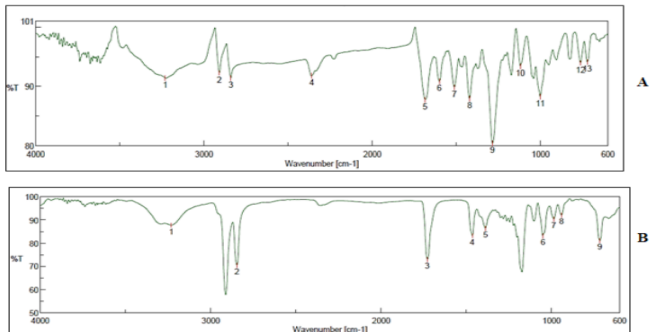

Fig. 8: FT-IR Spectrum of (A) Febuxostat pure drug (B) Febuxostat loaded microballoons

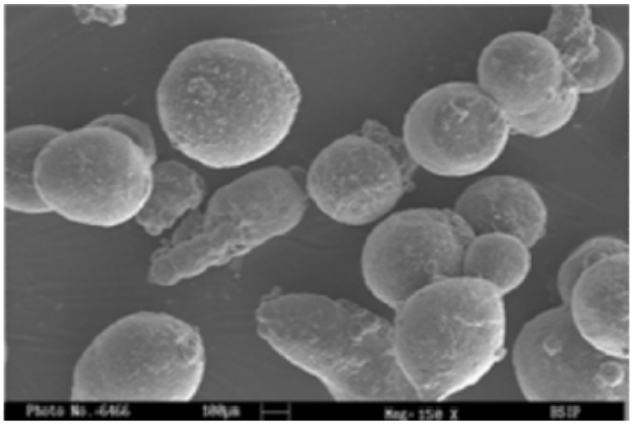

Fig. 9: SEM images showing size range of microballoons

was significant and reliable. As shown in Figs. 5 and 6 microballoons were discrete particle size with smooth surface texture with hollow space which is responsible for increased in buoyancy leads to increases in gastric retention time and better therapeutic effect.

Percentage (%) Yield

The %yield of the febuxostat loaded microballoons was found to be 95 ± 0.039 %.

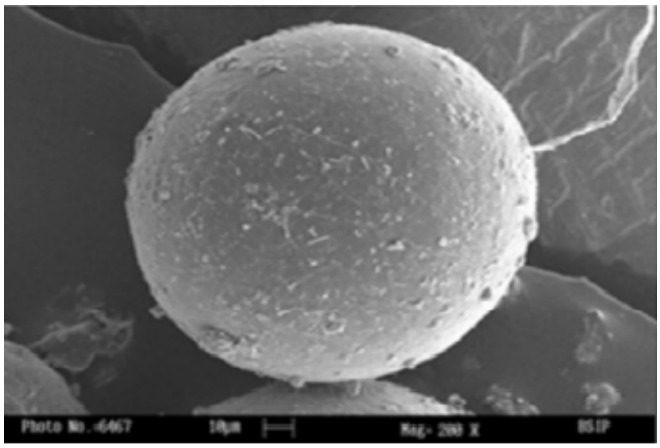

Fig. 10: SEM images showing smooth surface of microballoons

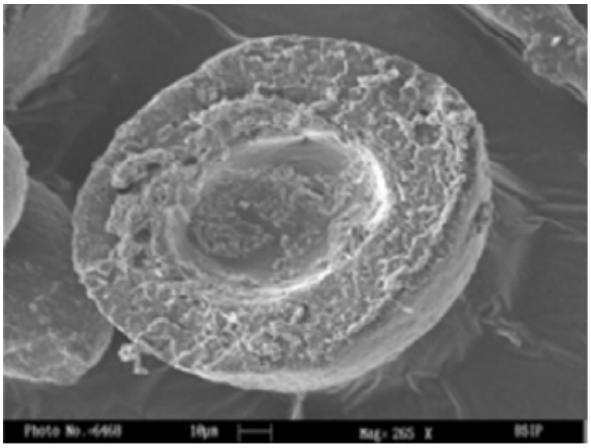

Fig. 11: SEM images showing hollow structure of microballoons

Table 8: Stability Study

Storage Condition	*Particle size (µm)*	*%EE*	*%Buoyancy*
At the time of Preparation	80.11 ± 0.349	83.25 ± 0.526	92.41 ± 0.57
Initial 40°C ± 2°C temperature and 75% ± 5% RH (15 days)	80.09 ± 0.256	82.89 ± 0.431	92.06 ± 0.352
Initial 40°C ± 2°C temperature and 75% ± 5% RH (30 days)	80.06± 0.712	82.42 ± 0.231	91.58 ± 0.645

(Mean±SD, n=3)

In-vitro Drug Release Study

In-vitro drug release analysis of febuxostat loaded microballoons and pure drug performed by USP dissolution test apparatus II paddle-style dissolution assembly, As compare to pure drug form febuxostat loaded microballoons facilitate maximum surface area for drug absorption. FEB-MBs is sustained release up to 12 hours of drug release 98.43 ± 0.543 % in the body, So Gastric retention time is increase due to buoyancy so that better therapeutic effect. The results obtained from *in-vitro* data revealed that the prepared microballoons had good buoyancy and better drug release shown in Fig. 7.

Characterization of Optimized Microballoons

FT-IR Study of Febuxostat Loaded Microballoons

FT-IR spectrum of febuxostat pure drug shown in Fig. 8 (A) and febuxostat loaded microballoons shown in Fig. 8 (B). The comparison of the spectrum of both peaks was described in Table 7. From the result, it can be observed that in the febuxostat loaded microballoons, no significant changes in the frequencies of the functional group compared with the FT-IR spectra of pure drug.

Scanning Electron Microscopy (SEM)

The morphological shape of microballoons has shown in Figs 9, 10, and 11. SEM images describe the discrete particle size with smooth surface texture with a hollow space and spherical shape in hollow microballoons. It also shows particle size < 200 µm, which confirms the micro size of the particle. Morphology shows the spherical shape and no aggregation of micro-size particles.

Stability Study

A stability study was performed to provide a conclusion that the formulation remains stable for a specific period. Stability study data shown in Table 8 shows measured Particle size, %EE and %buoyancy of the microballoons to ensure that the product remains unchanged. At the stability, chamber maintained at 40°C ± 2°C temperature and 75% ± 5% RH (Relative Humidity) for 15 days and 30 days as per ICH guideline, but after that, a slight change was observed. Particle size, % EE and %buoyancy were slightly change shown in table 8. Based on the stability, we can conclude that there was no significant change in microballoons of the optimized formulation after 30 days of storage at 40°C ± 2°C temperature and 75% ± 5% RH (Table 8). The prepared microballoons will float on the surface of the gastric fluid, releasing febuxostat in a sustained manner. In vitro studies indicate that microballoons may be a suitable febuxostat delivery mechanism because they increase bioavailability compared to conventional dosage forms.

Conclusion

In the current study, FEB-MBs were successfully formulated by a non-aqueous Solvent evaporation method. The concentration of Eudragit RS 100, HPMC K4 M, concentration of surfactant, and stirring speed play a crucial role in particle size, drug entrapment efficiency, and *in vitro* buoyancy. The formulation was optimized by the Box-Behnken design. Optimized batch shows 80.11 ± 0.349 µm particle size, 83.25 ± 0.526 %EE and 92.41 ± 0.57 %buoyancy. SEM image of formulation shows

discrete particle size with smooth surface texture with a hollow space and spherical shape, also shows particle size < 200 µm. The result of the *In-vitro* study shows an improved rate of the drug release from FEB-MBs compared with pure drugs. The stability study shows no significant change in microballoons of the optimized formulation after 30 days of storage as a ICH guideline. Finally, it is possible to conclude that microballoons drug delivery systems can be used as gastro-retentive drug delivery systems, reducing dosing frequency and improving patient compliance.

Abbreviations

API:	Active Pharmaceutical Ingredients
MB:	Microballoons
FEB-MBs:	Febuxostat loaded microballoons
HPMC:	Hydroxy propyl methyl cellulose
HCL:	Hydrochloric acid
KBr:	Potassium bromide
BCS:	Biopharmaceutical classification system
GIT:	Gastrointestinal track
ANOVA:	Analysis of variance
DOE:	Design of expert
USP:	United States Pharmacopeia
SD:	Standard deviation
%CDR:	Percentage cumulative drug release
FT-IR:	Fourier Transform Infrared Spectroscopy
SEM:	Scanning electron microscopy
%EE:	Percentage Entrapment Efficiency
RPM:	Rotation per minute

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