Febuxostat Loaded Microballoons: A Novel Approach for Gastric Retention

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Introduction

Microballoons are gastro retentive drug-delivery systems with a non-effervescent approach. Microballoons (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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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.

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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. 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°C 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.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Levels</th>
<th>Independent Variables</th>
<th>X1 Concentration of Eudragit RS 100 (mg)</th>
<th>X2 Concentration of HPMC K4 M (mg)</th>
<th>X3 Emulsifier concentration (%)</th>
<th>X4 Stirring speed (RPM)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low (-1)</td>
<td>Medium (0)</td>
<td>High (+1)</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td>Dependent Variables</td>
<td>Response</td>
<td>Y1</td>
<td>Particle size (µm)</td>
<td>Y2 % Entrapment efficiency</td>
<td>Y3 % Buoyancy</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1:** Optimization factors with levels

**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>
<thead>
<tr>
<th>Batch No.</th>
<th>Drug (mg)</th>
<th>Concentration of Eudragit RS 100 (mg) (X1)</th>
<th>Concentration of HPMC K4 M (mg) (X2)</th>
<th>Concentration of surfactant (%) (X3)</th>
<th>Stirring speed (RPM) (X4)</th>
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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]

\[
\% \text{ Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of drug and excipients}} \times 100
\]

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:

\[
\% \text{ Entrapment Efficiency} = \frac{\text{Calculated Drug Concentration}}{\text{Theoretical Drug Concentration}} \times 100
\]

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]

\[
\% \text{ Buoyancy} = \frac{\text{Weight of floating Microballoons}}{\text{Initial Weight of Floating Microballoons}} \times 100
\]

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 \(\lambda_{\text{max}}\) of Febuxostat is 315 nm so it is better to use methanol instead of using acetone for a calibration curve.
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 of 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.

\[
Y_1 \text{(Particle Size)} = + 61.63 + 15.22 *X_1 + 5.41 *X_2 - 0.13 *X_3 - 24.46 *X_4
\]

\[
Y_2 \text{(EE)} = + 73.50 + 6.83 *X_1 + 2.53 *X_2 - 0.31 *X_3 - 11.10 *X_4
\]

\[
Y_3 \text{(Buoyancy)} = + 79.28 - 3.65 *X_1 - 2.52 *X_2 - 12.37 *X_3 + 0.24 *X_4
\]

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

<table>
<thead>
<tr>
<th>Batch No.</th>
<th>Dependent variables</th>
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<tbody>
<tr>
<td></td>
<td>Particle size (µm) (Y1)</td>
</tr>
<tr>
<td>MB 1</td>
<td>35.02 ± 0.746</td>
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<tr>
<td>MB 2</td>
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<td>101.95 ± 1.234</td>
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<tr>
<td>MB 25</td>
<td>60.25 ± 0.828</td>
</tr>
</tbody>
</table>

Mean ± SD, n = 3

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

<table>
<thead>
<tr>
<th>Optimized batch</th>
<th>Experimental Value</th>
<th>Predicted Value</th>
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<tr>
<td>MB 28</td>
<td>Particle size (µm)</td>
<td>% EE</td>
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<td>80.11 ± 0.349</td>
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</tr>
</tbody>
</table>

(Means±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 febuxostat loaded microballoons

<table>
<thead>
<tr>
<th>Group</th>
<th>Pure Febuxostat drug</th>
<th>Febuxostat Loaded Microballoons</th>
</tr>
</thead>
<tbody>
<tr>
<td>O – H Stretching</td>
<td>3231</td>
<td>3232.11</td>
</tr>
<tr>
<td>C = N Stretching</td>
<td>2940.63</td>
<td>2846.42</td>
</tr>
<tr>
<td>COOH Group</td>
<td>1686.44</td>
<td>1728.87</td>
</tr>
</tbody>
</table>

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.

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

Percentage (%) Yield

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

Fig. 9: SEM images showing size range of microballoons
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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**References**
