Original Research Article

FORMULATION AND EVALUATION OF FLOATING SUSTAIN RELEASE PELLETS OF ANTI GOUT DRUG

.

ABSTRACT

Objective: The objective of this investigation was to formulate and evaluate effervescent pellets of febuxostat to achieve sustain release effect.
Place and Duration of Study: APMC College of Pharmaceutical education and research, Department of Pharmaceutics, Himatnagar-383001, between June 2019 and July 2021.
Materials and Methods: The gastroretentive effervescent pellets of febuxostat were formulated using Sodium CMC and HPMC K4M and HPMCK15M as a sustain release polymer. Pellets were prepared by extrusion- spheronization technique using microcrystalline cellulose as spheronizing agent and sodium bicarbonate and citric acid as a gas forming agent for effervescent pellets. The pellets were characterized with respect to their floating lag time, total buoyancy time and % cumulative drug release.
Results and Discussion: DSC study showed that there was no change in the melting endotherm of the drug and drug-polymers mixture which means drug and polymers were compatible with each other. The optimized formulation B14 exhibits a floating lag time 4.00±0.004 sec. and cumulative % drug release at 12th hour 99.58±. Scanning electron microscopy photomicrograph revealed that the surface was rough and pellets were spherical shaped in nature.
Conclusion: Febuxostat sustain release pellets was successfully formulated and evaluated as effervescent pellets with gas former agents and sustain release polymer HPMC K15.

Keywords: HPMC K15M, Effervescent, Febuxostat, Floating.

1. INTRODUCTION

From the past four decades Oral dosage forms have been developed due to their significant therapeutic advantages such as patient compliance, ease of patient administration and flexibility in formulation[1].Gastroretentive drug delivery system is an innovative approach for the novel drug delivery system in which the drug retained in the stomach for a prolonged period[2,3]. GRDDS is mostly appropriate for drugs that acts locally in a part of the gastrointestinal tract, drugs which are unstable in intestinal fluids, drugs having narrow absorption window and drugs that show poor solubility[4,5]. The multiparticulate FDDS was preferred over a single-unit system due to minimum inter and intrasubject variability in drug absorption and lower possibility of dose dumping[6].

FDDS are low density systems, which allows them to remain buoyant in the stomach for a prolonged period. Effervescent systems are widely employed technology in the

development of FDDS with buoyancy mechanism. In effervescent systems, carbon dioxide gas production occurs due to the reaction of bicarbonates and acid present in pellets, formed gas is entrapped in the polymers, which allows the systems to remain buoyant. The FDDS are efficiently used to design sustained drug delivery systems and improve the oral bioavailability of drugs.[7-9]

Target serum uric acid(sUA) levels do not achieve by the patients who treated with allopurinol, due to intolerability to allopurinol doses above 300 mg and patients with renal insufficiency dose reduction are required, while treated with febuxostat, rapid and considerable reductions in sUA levels. Compared with allopurinol-treated patients, patients receiving febuxostat 40 and 80 mg were more likely to achieve sUA concentrations less than 6 mg/dl.[10,11]

Febuxostat is a2- arylthiazole derivative, BCS class II drug having high permeability and low solubility. The Febuxostat decreasing serum uric acid by inhibiting xanthine oxidase with an in vivo inhibition k_i value less than one nanomolar and it potently inhibit both the oxidized and reduced forms of xanthine oxidase[12].

Although conventional oral dosage forms are widely used for the treatment of gout, but very poor bioavailability are observed in conventional dosage forms due to hepatic first pass metabolism.

Pellets, a multiparticulate system has numerous therapeutic and technological advantages over single unit dosage form like tablets. Hence pelletization of febuxostat reduces the risk of dose dumping and provides uniform distribution of drug up to 24 hrs.

Hence, the objective of present work is to formulate and develop gastroretentive effervescent floating pellets of febuxostat using extrusion spheronization technique

2. MATERIAL AND METHODS

2.1 Materials

Febuxostat was obtained as a gift sample from Spentica life science. HPMC K15M, Sodium CMC and Microcrystalline cellulose was procured from qualichem, vadodara. Citric acid was procured from purvi chemicals, Ahmedabad. All the studies were carried in distilled water.

2.2 Methods

2.2.1 Formulation of effervescent floating pellets

Floating pellets containing febuxostat were prepared using extrusion spheronization technique. The drug (80 mg), gas generating agent and pelletization aid quantity were mixed as per table 1. Sufficient amount of PVP K15/K30/K90 was slowly added in the powder mixture to achieve a consistency of the damp mass suitable for further extrusion spheronization processes. The extrudate of uniform size was produced with the extruder. The extrudate was then spheronized in a spheronizer with a rotation plate of regular cross hatch geometry for 10- 15 min at a rotation speed of 1500 RPM. The resultant pellets were air dried for 15 min.

Table 1. Formulation batches of effervescent pellets

Batch	MCC	Na.CMC	NaHCO3	HPMC K4	HPMC K15	PVP K15	PVP K30	PVP K90	Citric acid
1	2g	0.6g	0.9g	1.25g		2.50%			0.3g

2	2g	0.6g	0.9g	1.25g		5%			0.3g
3	2g	0.6g	0.9g	1.25g		7.50%			0.3g
4	2g	0.6g	0.9g	1.25g			2.50%		0.3g
5	2g	0.6g	0.9g	1.25g			5%		0.3g
6	2g	0.6g	0.9g	1.25g			7.50%		0.3g
7	2g	0.6g	0.9g	1.25g				2.50%	0.3g
8	2g	0.6g	0.9g	1.25g				5%	0.3g
9	2g	0.6g	0.9g	1.25g				7.50%	0.3g
10	2g	0.6g	0.9g		1.25g	2.50%			0.3g
11	2g	0.6g	0.9g		1.25g	5%			0.3g
12	2g	0.6g	0.9g		1.25g	7.50%			0.3g
13	2g	0.6g	0.9g		1.25g		2.50%		0.3g
14	2g	0.6g	0.9g		1.25g		5%		0.3g
15	2g	0.6g	0.9g		1.25g		7.50%		0.3g
16	2g	0.6g	0.9g		1.25g			2.50%	0.3g
17	2g	0.6g	0.9g		1.25g			5%	0.3g
18	2g	0.6g	0.9g		1.25g			7.50%	0.3g

2.2.2 Evaluation of pellets

2.2.2.1 Calibration curve

Calibration curve was taken in methanolic phosphate buffer pH 7.4 for that dissolve 10 mg of drug in 100 ml of methanolic phosphate buffer in a volumetric flask to get 100 µg/ml stock solution. This solution was further diluted to get solution in the concentration range of 1-10 µg/ml. Absorbance of these solution was determined spectrophotometrically at 314.87 nm (UV-1650, Pharmaspec, Shimadzu Ltd, Japan.)

2.2.2.2 Drug excipient compatibility study by Differential scanning calorimetry

Differential Scanning Calorimetry study were carried out with a differential scanning calorimeter (DSC 60 Shimadzu, Japan) under nitrogen flow. Samples each of 2 mg were accurately weighed using a santorius electronic microbalance and sealed in aluminum DSC pan and placed in the DSC cell. The DSC was previously calibrated for the temperature and enthalpy measurements in the standard way using melting of pure indium metal as a reference material. DSC runs were conducted over a temperature range of 50˚C to 300˚C at 10˚C /min under nitrogen flow rate of 40 ml/min. as reference empty aluminum pan was used.

2.2.2.3 Flow properties of pellets

For determination of flow from hopper to cavity used by using a funnel and calculated with equation 1, bulk and tapped density were calculated from bulk and tapped volume by using bulk and tapped density apparatus and by using those values Hausner's ratio and Carr's index were determined by equation 2 and 3.

$$\text{Angle of repose } \theta = \tan^{-1}\frac{h}{r} \quad (1)$$

Where h= Height of pile and r= radius of the circle

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \quad (2)$$

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad (3)$$

2.2.2.4 Particle size distribution

The particle size distribution of pellets was carried out by sieve analysis using mesh fractions 16/18, 18/20, 20/30, 30/44, and 44/60 for 5 min on a mechanical sieve shaker. The study was performed in triplicate for each batch of pellets.

2.2.2.5 Friability

Friability of the pellet formulations was determined using friabilator (Electrolab, Mumbai). 10 g of pellets were kept into friabilator and the percentage weight loss after 25 rpm for 4 min. was determined[13].

$$\text{Friability}=\frac{\text{Initial weight}-\text{final weight}}{\text{Initial weight}}\times 100 \quad (4)$$

2.2.2.6 Drug content

The drug content in each formulation was determined by taking floating pellets equivalent to about 100 mg of febuxostat, grounded and transferred into a volumetric flask containing 0.1 N HCl. The mixture was sonicated for 30 minutes to ensure complete extraction of drug in 0.1 N HCl. The solution was further filtered, diluted with appropriate amount of 0.1 N HCl and assayed spectrophotometrically at 314.187 mm [1,14,15]. (UV-1650, Pharmaspec, Shimadzu Ltd, Japan.) (n = 3).

% Drug content = {Weight of drug present in pellets (gm)/Weight of quantity of pellets (gm)} ×100

2.2.2.7 Buoyancy study

The time between the introduction of the pellets into the medium and its buoyancy to the upper one third of the dissolution vessel (floating lag time) and the time for which the formulation constantly floated on the surface of the medium (floating duration) were measured simultaneously. The 100mg of pellets were placed in a beaker filled with 50 ml 0.1N HCl. Temperature was maintained at 37ºC. The floating time of pellets was observed for 12hrs[15].

2.2.2.8 In vitro drug release studies

The drug release study was carried out using USP (type-II) paddle apparatus at 37 ± 0.5ºc and at 50 rpm using 900 ml of 0.1N HCl as a dissolution medium (n=3). Accurately weighed pellets were placed in each vessel of dissolution apparatus. 10 ml of sample solution was withdrawn at predetermined time intervals, filtered, dilute suitably and analyzed spectrophotometrically. Equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. The cumulative percentage drug release was calculated for 12hr.

2.2.2.9 Surface morphology

Scanning electron microscopy is the technique of choice for measuring the shape, size and surface morphology of the pellets to support visually the other qualitative and quantitative results.

3. RESULTS AND DISCUSSION

3.1 Spectroscopic studies

The λ max of febuxostat was found to be 314.87 nm. It obeyed Beer's law in the range of conc. 2-10µg/ml. Linear regression of absorbance on concentration gave equation y=0.831x + 0.019 with a correlation coefficient of 0.998 in methanolic Phosphate buffer pH 7.4 as indicated in figure 1.

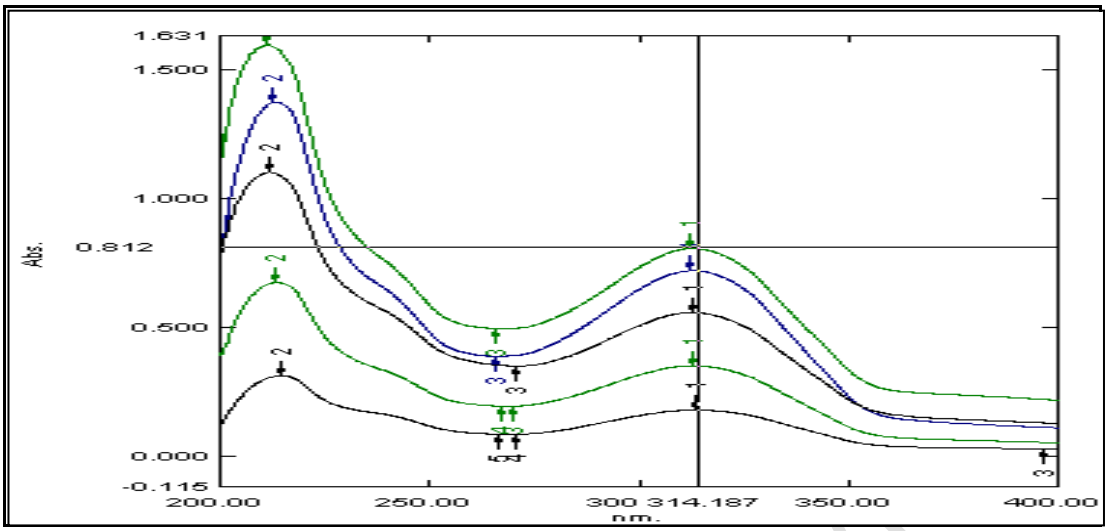

Fig. 1 Determination of λmax of Febuxostat

3.2 Drug-excipient compatibility study by DSC

DSC is a thermodynamic analytical technique used to compare the thermal behavior of the pure drug and the combination of drug and excipients. The DSC thermogram of febuxostat showed sharp endothermic peak at 211.54˚C shown in figure 2 . In the DSC data of mixture of febuxostat and excipients, the sharp endothermic peak was observed near to 200 ˚C. Melting endothermic peak of the drug was well observed with a slight change in term of broadening of peak or sifting toward the lower temperature. Thus these minor changes in the melting endothermic peak of drug could be due to the mixing of drug and excipients, which lowers the purity of each component in the mixture and may not necessarily indicating potential incompatibility. There was no change in the melting endotherm of the drug and drug-polymers mixture. Hence, it was concluded that drug and polymers are compatible with each other. (Figure 2).

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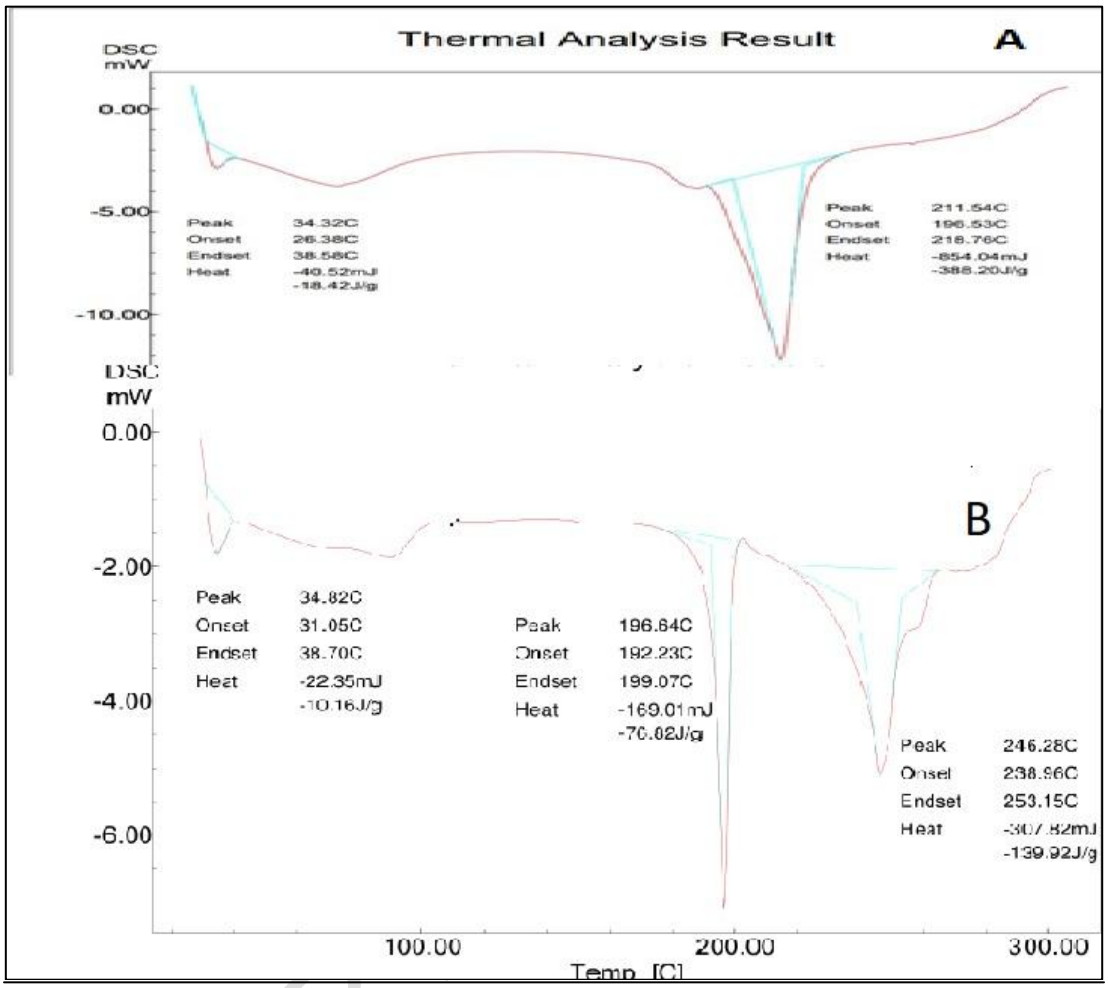

Fig. 2 Differential scanning calorimetry data of pure febuxostat (A) and drug-mixture (B)

3.3 Evaluation of prepared pellets

All batches of effervescent pellets were evaluated and obtained values indicated in table 2. The angle of repose, carr's index and hausner's ratio values were within range specified. Thus all pellets were found to be stable for further evaluation.

Table 2 . Evaluation of micromeritic properties of pellets

Batch	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index CI (%)	Hausner's Ratio	Angle of repose
1	1.02 ± 0.011	1.09±0.012	12.70 ± 0.040	1.14±0.04	26.73±0.32
2	1.03 ± 0.011	1.06±0.005	13.45 ± 1.89	1.13±0.020	27.03±0.09
3	1.08 ± 0.017	1.04±0.014	15.15 ± 1.07	1.14±0.012	26.85±0.16
4	1.077 ± 0.011	1.08±0.014	12.43 ± 1.06	1.14±0.013	26.32±0.32

5	1.078 ± 0.013	1.08±0.01	13.42 ± 1.04	1.15±0.013	26.03±0.03
6	1.09 ± 0.012	1.1±0.012	15.42 ± 1.88	1.14±0.01	27.02±0.09
7	1.08 ± 0.018	1.02±0.017	12.13 ± 1.04	1.12±0.01	27.01±0.02
8	1.04 ± 0.019	1.01±0.018	13.17 ± 1.85	1.13±0.02	26.03±0.02
9	1.06 ± 0.017	1.03±0.019	15.87 ± 0.51	1.14±0.03	27.96±0.05
10	1.069 ± 0.013	1.04±0.005	12.76 ± 0.55	1.15±0.04	25.01±0.01
11	1.09 ± 0.019	1.01±0.017	13.11 ± 0.50	1.16±0.06	25.53±0.02
12	1.04 ± 0.029	1.05±0.014	17.73 ± 0.95	1.17±0.05	24.75±0.03
13	1.04 ± 0.028	1.07±0.019	17.73 ± 0.95	1.11±0.04	23.02±0.01
14	1.08± 0.018	1.01±0.012	16.11±0.50	1.02±0.01	21.02±0.02
15	1.06 ± 0.012	1.09±0.014	15.76 ± 0.55	1.09±0.04	22.02±0.01
16	1.05 ± 0.015	1.12±0.012	15.17 ± 1.85	1.11±0.04	23.20±0.03
17	1.01 ± 0.016	1.05±0.01	12.42 ± 1.89	1.12±0.05	24.02±0.04
18	1.03 ± 0.010	1.03±0.015	13.70 ± 0.040	1.14±0.06	25.01±0.01

Determination of % drug content

The results of %drug content were shown in table 3. The values were in range 85.21±1.31 to 95.49±0.99. batch no. 2 and 10- 18 were qualified for the further evaluation.

Table 3. Evaluation of Friability, average particle size and drug content of pellets

Batch	Friability (%)	Average particle Size (µm)	Shape	Drug Content (%)
1	0.74±0.16	998	Oval	89.80±1.69
2	0.72±0.33	1100	Oval+Spehrical	91.01±1.55
3	0.73±0.25	1010	Oval> Spherical	88.96±1.80
4	0.79±0.013	1060	Oval and long	87.16±1.96
5	0.82±0.02	1069	Oval	89.80±1.32
6	0.7±0.01	1020	Oval +Spherical	86.35±1.58
7	0.92±0.05	1100	Oral> Spherical	88.47±1.71
8	0.95±0.02	1125	Oval> Spherical	87.38±1.64
9	0.9±0.07	1088	Oval and long	85.21±1.31
10	0.53±0.08	1225	Spherical >Oral	93.61±1.55

11	0.43±0.16	1180	Spherical >Oral	91.26±1.46
12	0.51±0.15	1175	Spherical >Oral	90.72±0.981
13	0.43±0.14	1170	Spherical >Oral	91.26±1.49
14	0.32±0.01	1165	Spherical	95.49±0.99
15	0.35±0.02	1170	Spherical	90.72±0.97
16	0.37±0.01	1078	Spherical >Oral	93.57±1.57
17	0.34±0.03	1120	Spherical >Oral	91.27±1.89
18	0.33±0.05	1220	Spherical >Oral	91.01±1.55

3.4 *In vitro* buoyancy studies

In vitro buoyancy studies were performed on feboxostat pellets. The Floating lag time and total floating time of pellets are indicated in table 3. As we change the polymer grade from HPMC K4M to HPMCK15M, the buoyancy lag time has been decreased. HPMC K15M with 5% PVPK30 concentration of binder provides maximum total floating time. According to data we optimized the batch having minimum floating lag time(Sec.) and maximum total floating time(hr.) and that was batch no. 14.

Table 3. Buoyancy test for various febuxostat formulations

Batch	Floating lag time (sec)	Total floating time (hr)
1	11.25±0.20	8.2±0.02
2	12.26±0.19	7.25±0.04
3	13.08±0.11	7.55±0.07
4	10.16±0.23	7.16±0.01
5	8.25±0.20	9.5±0.04
6	8.2±0.14	9.75±0.09
7	9.16±0.23	8.7±0.01
8	10.33±0.31	7.6±0.06
9	12.41±0.31	8.1±0.04
10	5.38±0.27	8.27±0.02
11	6.33±0.23	9.05±0.02
12	6.38±0.30	8.2±0.01
13	7.28±0.20	10.01±0.06
14	4.00±0.004	11.5±0.03

15	6.02±0.02	9.2±0.01
16	6.01±0.08	8.5±0.07
17	7.2±0.14	7.15±0.01
18	7.26±0.19	7.25±0.4

From all above evaluation, formulation batch having minimum floating lag time **(**4.00±0.004 sec.), maximum total floating time (11.5±0.03 hr.) and drug content (95.49±0.99%) optimized for *invitro* drug release and surface morphology.

EVALUATION OF OPTIMIZED BATCH

In vitro dissolution studies

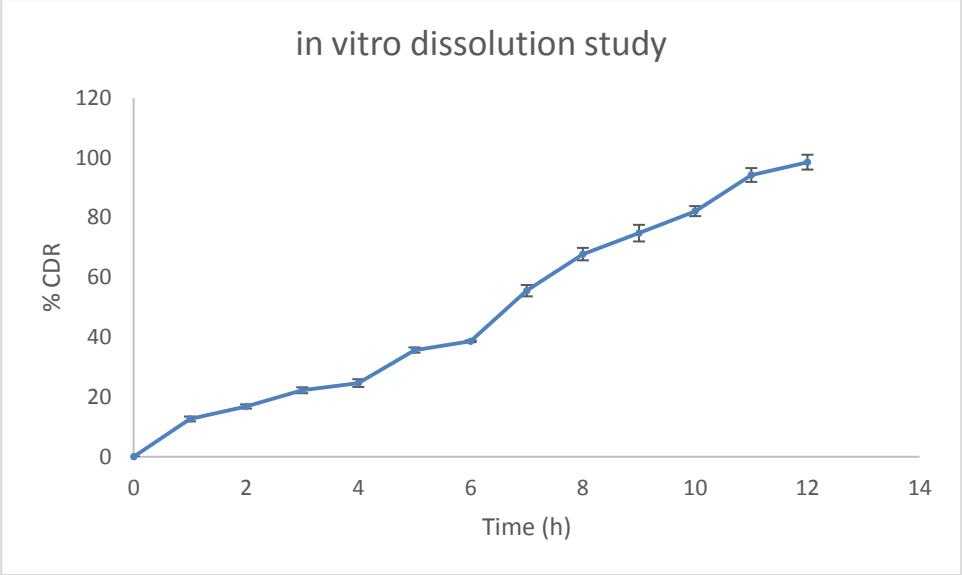

Fig. 3. Dissolution profile of optimized formulation

Surface Topography (SEM analysis)

Photomicrographs of pellets (Figure 4) revealed that the surface was rough and the pellets were spherical in nature, which having size less than 1 mm, were taken using a scanning electron microscope **(JSM7600F Joel, Tokyo, Japan)** for visualization of pellet surface morphology.

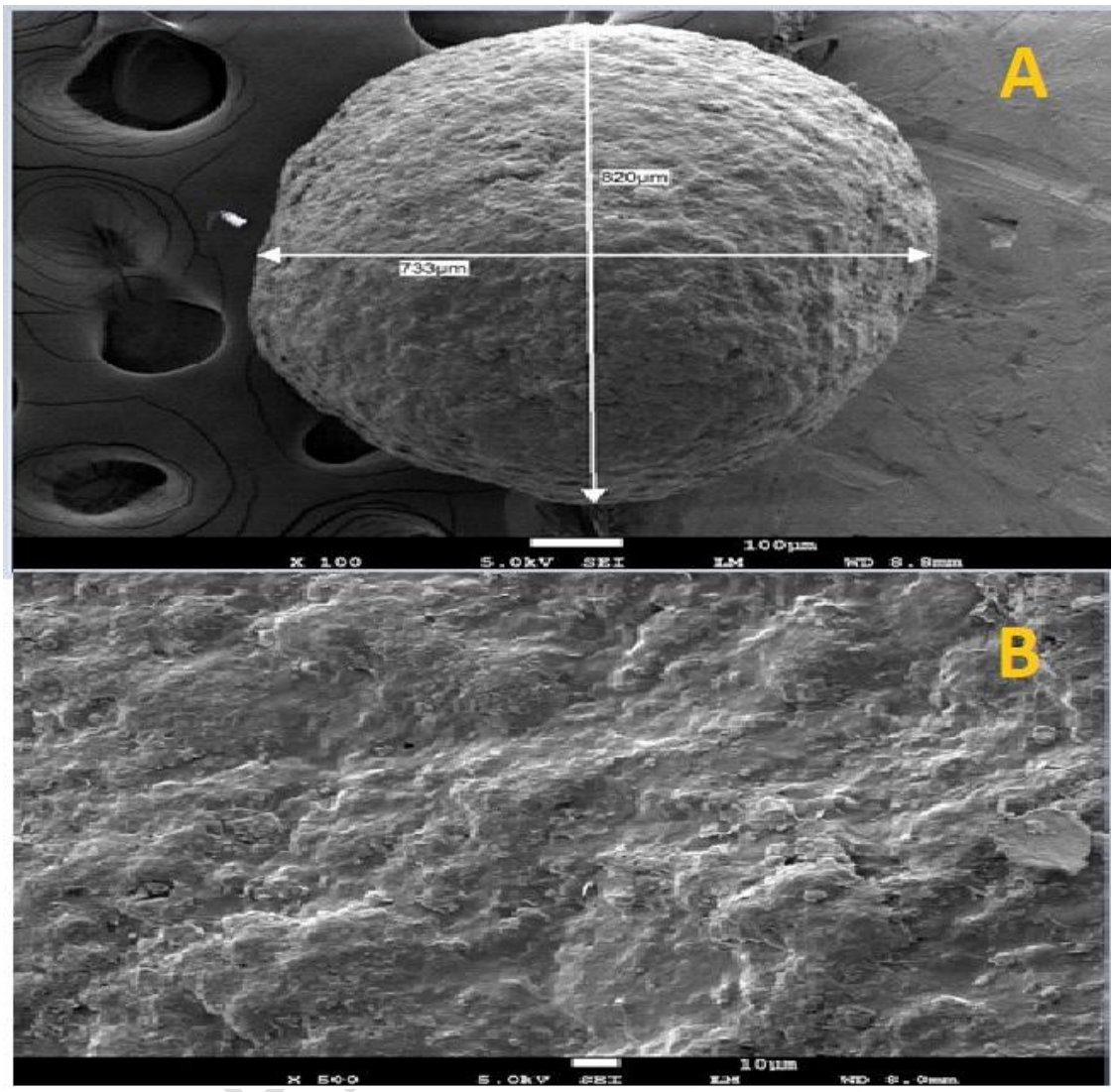

Fig. 4. SEM photograph of floating pellets with drug {In 100 x(A) and 500 x(B)}

4. CONCLUSION

The Effervescent floating pellets of febuxostat was prepared and evaluated successfully by extrusion spheronization method using gas generating agent and sustain release polymer. It was found that change in polymer grade and concentration of binder- PVP, also change in buoyancy lag time and total floating time. It was concluded that HPMC K15M with 5% PVP K30 binder concentration provide maximum total floating time and minimum lag time The optimized formulation batch no. 14 showed drug release of 98.54% within 12 h. SEM study near to 1mm confirmed that the prepared formulation was spherical in nature.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and

country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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