RESEARCH

Optimizing pulsatile release of febuxostat for managing gout flares: a chronotherapeutic approach

Khyati Parekh[1], Vaishali Thakkar[1]*, Arjun Joshi[1], Chetan Sojitra[2], Saloni Dalwadi[1] and Hardik Rana[1]

Abstract

Background Chronic conditions such as nocturnal asthma, cardiac disorder, diabetes mellitus, joint pain and inflammation, and hypercholesterolemia necessitate a treatment strategy that can be planned in accordance with the disease's biological clock. The early morning spike in blood plasma uric acid was associated with gout. The treatment of these symptoms may not be feasible with immediate release formulations. Modified release formulations allow for controlled and consistent levels of medication in plasma throughout the day, but do not provide additional therapeutic levels when symptoms worsen. A chronotherapeutic system of febuxostat characterized by a time of no release (lag time) followed by a quick and complete release, can be designed to overcome this. The aim of the present study was to design a pulsincap of febuxostat to release the medication as per chronological conditions.

Results The study commenced with the optimization of the capsule body coating to maintain its integrity over a 12-h period. Subsequently, polymers for immediate and sustained release tablets were screened, and the prepared tablets were subjected to physicochemical evaluation. For the optimization of the erodible plug, a 3^2 full factorial design was employed, leading to the creation of nine different polymer combinations. The response curves of HPMC K15M demonstrated a negative impact on swelling index and lag time, while displaying a positive effect on hardness. In contrast, the aloe vera, guar gum mixture exhibited significant effects on swelling index and lag time, but negatively influenced hardness. Diagnostic plots and ANOVA were utilized to confirm the significance and goodness of fit of the model. An optimized formulation was then developed based on the desirability plot. The formulated capsule, consisting of 91.71 mg of HPMC K15M and 101.56 mg of aloe vera, guar gum mixture, exhibited promising properties. Notably, it demonstrated a 70.69% swelling rate, a hardness of 5.78 kg/cm^2, and an 8.57-h lag time. The pulsincap successfully met the requirement of immediate release within the first hour, followed by a pulsatile release with a lag time lasting for at least 8–10 h.

Conclusions In conclusion, the formulation effectively reduces the threat of gout flares and enhances patient compliance due to its night-time dosing convenience.

Keywords Febuxostat, Pulsincap, 3^2 full factorial design, Chronotherapeutic drug delivery system

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Background

Gout, an inflammatory arthritis, is widely recognized as the most prevalent form of such conditions. Notably, acute gout flares are acknowledged as one of the most excruciating occurrences encountered by individuals [1]. Deposition of monosodium urate crystals in joints and soft tissues following chronic hyperuricemia leads

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to gout [2]. It is defined as an elevated serum uric acid (SUA) level above 7 mg/dl in men and above 6 mg/dl in men and women [3]. The most commonly affected is the metatarsophalangeal joint called podagra at the base of the big toe. Other joints affected include heels, knees, wrists, and fingers [4]. Lower body temperature, relative nocturnal dehydration, and the nocturnal drop in cortisol levels have been hypothesized to increase the risk of gout attacks at night. The potential involvement of sleep apnea, which is common among obese men with multiple comorbidities, a typical profile of gout patients, is another explanation for the nocturnal onset. Hypoxia associated with sleep apnea can increase nucleotide turnover, resulting in the production of purines that are metabolized to uric acid, causing hyperuricemia in these patients [1].

Because of the steepest rise in SUA levels in the early morning in gout, immediate release (IR), sustained release (SR), or controlled release (CR) is not more effective. Theoretically, zero-order drug release from modified release dosage forms leads to controlled and constant drug levels in plasma throughout the day. However, this does not provide additional therapeutic levels during periods of increased symptoms, and unwanted plasma drug concentrations at other times of the day may produce adverse effects with little benefit to the patient. Potential therapeutic options include chronopharmaceutical formulations based on time-controlled drug delivery systems for optimizing therapy in terms of safety, patient compliance, and efficacy [5]. Pulsatile drug delivery is more effective in delivering the right drug at the right time at the action site. After the pre-programmed "lag period," the medication is released quickly [6]. The rhythms that occur once every 24 h are known as circadian. Circadian rhythms are synchronized with the body's sleep and arousal cycles and last approximately 24 h. Coordination of drug delivery with such biological clocks and rhythms is called chronotherapy [7]. Chronotherapy is a method for increasing the drug's effectiveness when it is needed most. Chronotherapy is beneficial for the better management of conditions such as nocturnal asthma, ulcers in the gastrointestinal tract, cardiac disorders, diabetes mellitus, joint inflammation and pain, hypercholesterolemia, cancer, and hormone secretion, for which the treatment method can be tailored to the disease's biological clock [8].

A pulsatile drug release system refers to a mechanism that enables the regulated and precise release of active medicinal ingredients in either single or sequential pulses, at specific intervals. Pulsatile systems refer to drug delivery methods that are regulated by time, allowing for autonomous regulation of the lag time regardless of external conditions such as pH, enzymes, gastrointestinal motility, and so forth. A pulsatile release profile

is distinguished by a period of no release, known as lag time, succeeded by a swift and comprehensive release. By using the pulsatile drug delivery system, it is possible to achieve an appropriate timing for the plasma peak, leading to a reduction in the frequency of daily doses. Additionally, the utilization of this system can help prevent issues related to saturable first-pass metabolism and the development of tolerance [5, 7].

The current study aims to explore the potential of utilizing pulsincap technology for the delivery of febuxostat. Treatment with febuxostat shows promising results with fewer disease complications [9]. Febuxostat is a novel selective xanthine oxidase inhibitor (XOI). It is typically metabolized by the liver, while renal elimination plays a minor role. As a non-competitive XOI, febuxostat appears preferable to allopurinol because of its increased potency, specificity, and reduced dependence on renal excretion. The chronotherapeutic delivery will be beneficial in treatment of gout flares. For efficient drug release from the capsule, the pulsatile principle was implemented. Body of capsule was coated with ethyl cellulose. Immediate and sustained release tablets with enhanced drug solubility by solid dispersion were prepared. 3^2 full factorial design was used for optimizing erodible plug polymers. The micromeritics property of the powder mixes was evaluated. The immediate and sustained release tablets were evaluated for various parameters including drug release. Erodible plug was evaluated for swelling index, hardness, and lag time along with other parameters. The impact of polymer ratio on swelling index, hardness, and lag time was evaluated. Optimized erodible plug along with immediate and sustained released tablets was filled in the capsule and evaluated for drug release.

Methods
Materials
Febuxostat was gifted by Zydus Healthcare Ltd., Ahmedabad. Crospovidone was obtained from ACS chemicals, Ahmedabad. Ethylcellulose was obtained from Ultrapure lab chem, India. Hydroxy propyl methyl cellulose (HPMC) K15M was purchased from Otto Chemie Pvt. Ltd., Mumbai. Soluplus was purchased from BASF Pvt. Ltd., Mumbai. Aloe vera powder was purchased from Neelkanth Finechem, Jodhpur. Guar gum was obtained from H.B gum industries Pvt. Ltd., Kalol.

Solubility enhancement of febuxostat
Preparation of solid dispersion
Solid dispersion was prepared by physical mixing. The powders were passed through a 44# sieve and weighed quantity of drug and soluplus was taken in a glass mortar pestle in different ratios (1:1, 1:2, and 1:3). The powder

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mixtures were triturated for half an hour [10]. The samples were stored in a screw-capped glass vial until use.

Phase solubility study

According to Higuchi and Connors, the phase solubility study of febuxostat was performed [11]. A surplus of febuxostat/soluplus dispersion was added to acetate buffer with a pH of 4.5 and phosphate buffer with a pH of 6.8. The solution was shaken for 24 h at 100 rpm in an orbital shaker until equilibrium was reached. After filtering the sample, absorbance was measured at λ_{max} (314 nm) against a suitable blank solution using an ultraviolet–visible (UV–VIS) spectrophotometer. The following equation determined the thermodynamic parameter of Gibbs free energy ($\Delta G°$).

$$\Delta G° = -2.303RT \log \left(\frac{Sc}{So} \right)$$

where $\Delta G°$ = Gibbs free energy of transfer; R = Gas constant (8.314 J/K-mole); T = Temperature in kelvin; Sc/So = molar solubility ratio of febuxostat/soluplus dispersion [12].

Evaluation of solid dispersion

Micromeritic properties of solid dispersion The flow properties of solid dispersion are important in the pharmaceutical industry, especially in the blending of powders, compression of tablets, and the filling of capsules. Several parameters were used to measure the flow properties of the prepared solid dispersion, such as the bulk density, the tapped density, the angle of repose, Carr's index, and Hausner's ratio.

1. Bulk density

It is the mass-to-bulk volume ratio. Bulk density may influence dissolution and other properties; it is dependent on particulate size, shape, and adhesion tendency. By placing a known mass in a graduated 10 ml measuring cylinder, the bulk density was determined. The cylinder was lowered three times at a rate of two seconds from a height of one inch. The following equation calculated the bulk density,

$$\rho_b = M/V_b$$

where ρ_b = Bulk density; M = Mass of powder; V_b = Bulk volume of powder.

2. Tapped density

The measurement of tapped density is employed in order to ascertain the packing arrangement and flow characteristics. The tapped density refers to the measurement of the volume of a powder sample obtained by the process of tapping, which involves utilizing a measuring cylinder to contain the predetermined amount of powder. The following equation calculated the tapped density,

$$\rho_t = M/V_t$$

where ρ_t = Tapped density; M = Mass of powder; V_t = Tapped volume of powder.

3. Carr's index

The Carr's index is calculated as the percentage of powder compressibility, which is derived from the comparison between bulk density and tapped density. The following equation was used,

$$Carr's\ index(\%) = [(\rho_t - \rho_b)/\rho_t] \times 100$$

where ρ_t = Taped density; ρ_b = Bulk density.

4. Hausner's ratio

The Hausner's ratio serves as a quantitative measure for evaluating the flowability of powders. The ratio being referred to is the relationship between tapped density and bulk density.

$$Hausner's\ Ratio(\%) = \rho_t/\rho_b$$

where ρ_t = Tapped density; ρ_b = Bulk density.

5. Angle of repose

The angle of repose is defined as the possibility of the maximum angle between the surface of the pile and the horizontal plane. The fixed funnel method was used to measure the angle of repose. It has been used for the characterization of interparticle friction between the particles.

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

where h = Height of the pile; r = Radius of a pile [13].

Fourier transform infrared spectroscopy (FTIR) Spectroscopy was conducted using FTIR spectrophotometer (Spectrum GX-FT-IR, PerkinElmer, USA) for the untreated febuxostat and solid dispersion. The spectrum was recorded in the range of 4000–400 cm^{-1}. The procedure consisted of dispersing a sample in KBr followed by gentle mixing. The spectrum was scanned at a resolution of 0.15 cm^{-1} and scan speed was 20 scan/s.

Differential scanning calorimetry (DSC) DSC (DSC-PYRIS-1, Phillips, Netherlands) was used to study the thermal behavior of the untreated febuxostat and solid dispersion. The experiments were performed in a dry nitrogen atmosphere. The samples (2–4 mg) were heated in hermetically sealed flat-bottomed aluminum pans under nitrogen flow (20 mL/min) at a scanning rate of 10 °C/min from 25 to 200 °C. Empty aluminum pans were used as the reference standard. DSC spectra were recorded in an aluminum pan at a scanning rate of 20 °C/min in an atmosphere of nitrogen gas (50 ml/min) [14].

In vitro dissolution rate studies on solid dispersions Solid dispersions equivalent to 40 mg of febuxostat were placed in 900 ml of acetate buffer pH 4.5 (to simulate stomach condition) and phosphate buffer pH 6.8 (recommended media as per U.S.FDA) in USP apparatus II for in vitro dissolution rate studies. The paddle was used to maintain 75 revolutions per minute. Throughout the investigation, the temperature of the dissolution medium was maintained at 37 ± 0.5 °C. At regular intervals, approximately 5-ml samples were collected. To maintain the sink's condition, an equal volume of new dissolution medium was added. The withdrawn aliquots were filtered through 0.45 Whatman filter paper, diluted appropriately, and measured for febuxostat at λ_{max} (314 nm) using an UV–VIS spectrophotometer. The dissolution experiments were repeated three times [15, 16].

Development of pulsincap for febuxostat

Pulsincap was manufactured through four stages. (1) Coating of capsule body, (2) Preparation of febuxostat tablets (SR and IR), (3) Optimization of erodible plug to achieve required latency time, and (4) Filling/assembly of tab-SR, erodible plug, and tab-IR into a coated capsule.

Coating of capsule body and optimization

Selecting hard gelatin capsules of the appropriate size, lids and bodies were then separated. As a plasticizer, dibutyl phthalate was combined with ethyl cellulose in methanol to create the coating solution. Only capsule bodies were permitted to be dipped in the coating solution. To meet the requirements of the chronotherapeutic drug delivery system, the number of coatings was optimized to maintain capsule integrity for at least 12/14 h. The integrity of the coated capsule was tested by soaking it in 900 ml of acetate buffer (pH 4.5) for 2 h, followed by phosphate buffer (pH 7.4) for 12 h [17].

Preparation of febuxostat tablets (SR and IR)

The direct compression method was used to prepare SR and IR tablet of febuxostat using various polymers like HPMC K15M, HPMC K100M, crosspovidone, and sodium starch glycolate. All the excipients were passed through 60 mesh sieve separately. The ingredients were weighed and mixed uniformly. The process of tablet compression involved the utilization of flat-faced punches within a rotary tablet punching machine. The compression force was modified in order to sustain the hardness within the range of 3–6 kg/cm^2. Polymers were selected based on evaluation parameters. Composition of tablets is depicted in Table 1.

Evaluation of prepared SR and IR tablets

All the tablets were evaluated for pre-compression parameters. In vitro dissolution was performed using USP apparatus II. The media for SR tablets were chosen as phosphate buffer pH 6.8 and 7.4, whereas acetate buffer pH 4.5 was used for IR tablets.

1. Tablet dimensions

Thickness and diameter were measured using a calibrated Vernier caliper. Three tablets of each formulation were picked randomly, and thickness was measured individually [18].

Table 1 Composition of tablets (SR and IR) containing febuxostat

Batch	Febuxostat/soluplus (mg)	HPMC K15M (mg)	HPMC K100M (mg)	Lactose (mg)	Crospovidone (mg)	Sodium starch glycolate (mg)
S1	75	75	–	–	–	–
S2	75	–	75	–	–	–
S3	75	37.5	37.5	–	–	–
S4	75	37.5	–	37.5	–	–
R1	45	–	–	45	10	–
R2	45	–	–	45	–	10

2. Hardness

Tablet hardness refers to the magnitude of force required to fracture a tablet during diametrical compression, as measured by the Monsanto hardness tester. A total of six tablets from each batch were subjected to testing, wherein the average hardness of the tablets was determined. It is measured in kg/cm^2.

3. Weight variation

This test was conducted by randomly selecting and weighing 10 tablets from each batch, and calculating the average weight.

$$\% \text{of weight variation} = \big(\text{Individual weight} \\ - \text{Average weight/Average weight}\big) \\ \times 100$$

4. Friability

Each set of 6.25 g tablets was placed in the revolving drum (25 rpm) of a Roche friability apparatus, which subjected the tablets to rolling and repetitive shock caused by free-fall within the apparatus. The tablets were removed after four minutes, dedusted, and reweighed. The weight was then recorded, and the friability was computed as a percentage of weight loss. Each experiment was repeated three times.

$$\% \text{Friability} = \big(\text{Tablet weight before friability} \\ - \text{Tablet weight after friability/Tablet weight after friability}\big) \\ \times 100$$

5. Disintegration time of IR tablets

The disintegration apparatus was used to analyze the disintegration of IR tablets. As a medium, 900 ml of acetate buffer pH 4.5 to replicate gastric conditions and phosphate buffer pH 6.8 (U.S.FDA-approved media) were kept at 37 ± 0.5 °C. A total of six tablets, denoted as = 6, selected at random, were introduced into individual glass tubes and subsequently subjected to operation. The disintegration time should be duly recorded to represent the average duration necessary for tablets to completely disintegrate. It is imperative that no residue be left behind on the sieve.

6. Drug content of prepared SR and IR tablets

A total of six tablets were subjected to crushing and subsequent weighing in this study. A quantity of

40 mg of powder was dissolved in methanol and subsequently subjected to filtration using a Whatman filter paper. The resulting filtrate was then subjected to analysis for drug content at the wavelength of maximum absorption (λ_{max}) of 314 nm, utilizing a UV–VIS spectrophotometer.

7. Comparison of prepared formulation with marketed formulation

Comparison of dissolution profile of febuxostat formulation of the optimized batch with marketed formulation (40 mg febuxostat tablet) (FEXANTO 40 mg ER and FEBUVEL 40 mg IR) was carried out. In vitro drug release study of the marketed formulation was carried out using USP apparatus II, at a speed of 75 rpm using 900 ml of dissolution media phosphate buffer pH 6.8 and 7.4 for SR and acetate buffer pH 4.5 for IR at 37 ± 0.5 °C.

Selection of polymers for erodible plug

A study was conducted to prepare an erodible plug for sealing the capsule body. This was achieved by compressing different polymers, namely HPMC K15M, guar gum, and aloe vera using various punches and dies on a rotary tablet press. The thickness and hardness values of the erodible plug were intentionally varied during the experimentation process. The erodible plug was subsequently inserted into the interior of a gelatin capsule that had been coated. Polymers for erodible plug were selected based on hardness, friability, swelling index, % erosion, and lag time [18].

Evaluation of polymers for erodible plug

Pre-compression parameters and post-compression parameters such as hardness and friability were performed.

1. Swelling index of erodible plug

Erodible plugs were weighed individually (W_1) and kept at pH 4.5 for 2 h, 6.8 for 3 h followed by pH 7.4 for the remaining time in a petri dish. The erodible plugs were removed from the petri dish after each hour, and excess surface water was removed carefully using tissue paper. The swollen erodible plug was then reweighed (W_2), and the swelling index was calculated using the following formula,

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$$\%\text{Swelling Index} = \frac{W_2 - W_1}{W_2} * 100$$

2. % Erosion of erodible plug

Initial weight of plug was noted down (W_1). Swollen plugs were dried at 60 °C for 24 h in an oven, kept in a desiccator for 48 h and reweighed (W_3). % matrix erosion was calculated using the following formula [19]

$$\%\text{Matrix Erosion} = \frac{W_1 - W_3}{W_3} * 100$$

3. Determination of lag time

The determination of lag time was conducted by employing an SR tablet and an erodible plug, followed by the assessment of in vitro drug release using a coated capsule body. The capsule body was hermetically sealed using a cap that is soluble in water. The release of the drug was monitored in an acetate buffer with a pH of 4.5 for a duration of 2 h. This was followed by a phosphate buffer with a pH of 6.8 for a duration of 3 h. Finally, the release was observed in a phosphate buffer with a pH of 7.4 for the remaining hours. The USP apparatus II was employed for this investigation. Aliquot samples were withdrawn at each hour for 12 h, replaced with fresh media and analyzed spectrophotometrically [20].

Optimization of erodible plug

3^2 full factorial design was chosen to statistically optimize the polymer concentration of erodible plug. The employed methodology facilitated the identification of key factors and optimal combinations that effectively fulfill the necessary characteristics of erodible plugs. Table 2 presents the recorded values of the formulation parameters, in both their actual and coded forms, as part of the comprehensive 3^2 full factorial design. The independent variables chosen for this study were the concentration of HPMC K15M (X_1) and the concentration of a 1:1 mixture of aloe vera and guar gum (X_2). These variables were investigated at three different levels, namely -1, 0, and $+1$. To generate the experimental runs, a 3^2 full factorial design was employed using design expert 11 software. This resulted in a total of nine experimental runs. The erodible plugs were fabricated through the process of direct compression, in accordance with the experimental runs outlined by the software. Subsequently, these plugs were assessed for their percentage swelling index (Y_1), hardness (Y_2), and lag time (Y_3) [17].

The present study employed the Design Expert software to conduct multiple regression analysis (MLR) and analysis of variance (ANOVA). The objective was to investigate the relationship between two independent variables, namely X_1 and X_2, and three dependent variables, namely Y_1, Y_2, and Y_3, within a factorial design. The selection of the optimal mathematical model involves considering the outcomes of MLR, specifically the correlation coefficient and coefficient values, as well as ANOVA, which includes the Fisher's ratio and associated *P* values. These metrics are utilized in the decision-making process to determine the most suitable model.

The selection of the most appropriate mathematical model was made by evaluating various statistical parameters, such as the coefficient of variation (CV), the multiple correlation coefficient (r^2), the adjusted multiple correlation coefficient (adjusted r^2), and the predicted residual sum of square (PRESS). This evaluation was conducted using the design expert® software. The PRESS metric is utilized to assess the goodness of fit of a model to the given data. It is desirable for the chosen model to have a relatively small PRESS value compared to the other models being evaluated.

Linear model:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2$$

Table 2 Actual and coded values of formulation parameters for 3^2 full factorial design

Independent variables	Coded and actual values		
	−1	**0**	**+1**
Concentration of HPMC K15M (mg) (X_1)	80	90	100
The concentration of a 1:1 mixture of aloe vera and guar gum (mg) (X_2)	80	90	100
Dependent variables			**Constraints**
$Y_1 =$ Swelling index (%)			55–75%
$Y_2 =$ Hardness (%)			> 5
$Y_3 =$ Lag time (h)			8–10 h

Quadratic model:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2$$
$$+ \beta_{12} X_1 X_2 + \beta_3 X_1^2 + \beta_4 X_2^2$$
$$+ \beta_5 X_1 X_2^2 + \beta_6 X_1^2 X^2$$

where β_0 is the intercept representing the arithmetic average of all quantitative outcomes of factorial runs; β_1 and β_2 are the coefficients computed from the observed experimental values of Y, and X_1 and X_2 are the coded levels of the independent variable(s). The terms $X_1 X_2$ and X_1^2 represent the interaction and quadratic terms, respectively. The statistical validity of the polynomials was established based on ANOVA; subsequently, the feasibility and grid searches were performed to locate the composition of the optimum formulation.

Validation of experimental design
The validation of the experimental design was conducted by determining the relative error through the utilization of the following equation formula,

$$\text{Relative Error (\%)} = \frac{\text{Predicted value} - \text{Practical value}}{\text{Predicted value}}$$

A relative error of less than 10% is expected to confirm the preciseness of the design.

Fabrication of optimized formulation
A formulation that has been optimized was prepared by utilizing concentrations of erodible plug weight that have also been optimized. The final formulation was fabricated by filling the SR tablet and optimized erodible plug in coated capsule body. IR tablet was placed on the erodible plug and should conform to the coated capsule body. Subsequently, the capsule body, which had been previously coated, underwent the process of being hermetically sealed with an uncoated cap. The formulation that had been optimized was subjected to in vitro dissolution studies, as previously described.

Stability studies of optimized formulation
Stability studies were performed for optimized formulation. A sufficient quantity of capsules was carefully placed into glass bottles and sealed with a rubber cork. These bottles were subsequently placed inside stability chambers that were meticulously regulated at a temperature of 40 ± 2 °C, along with a relative humidity of 75 ± 5%. At different time intervals, samples were collected and analyzed for in vitro drug release.
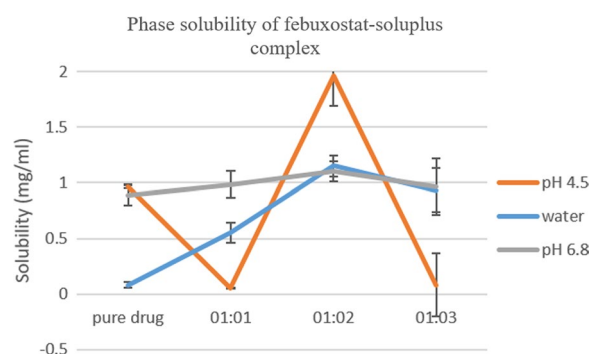

Fig. 1 Phase solubility study of solid dispersion

Results
Solubility enhancement of febuxostat
Phase solubility study
This study was performed to visualize the effect of polymer in different concentrations. The solubility was taken in acetate buffer 4.5 and phosphate buffer pH 6.8 as shown in Fig. 1. Solubility significantly increases up to a specific value after which it suddenly decreases. The phase solubility diagram corresponds to A_N-type profiles. The maximum solubility of febuxostat was observed in 1:2 ratio of solid dispersion which indicates 24.14-fold increase in acetate buffer pH 4.5 and 1.25-fold increase in phosphate buffer pH 6.8. The enhancement in solubility might be due to the surfactant behavior of soluplus that decreases the surface tension and increases the solubility.

Evaluation of solid dispersion
Pre-compression studies were performed which concluded better flow properties of solid dispersions as compared to pure drug.

Fourier transform infrared spectroscopy Numerous studies have consistently demonstrated that the interaction between drugs and polymers can exert a significant influence on the stability of the drug as well as its release characteristics from the formulation [21, 22]. The absorption bands of febuxostat in FTIR spectra were observed at 2238.86 cm^{-1} due to C≡N stretching, 1710 cm^{-1} due to C=O stretching, 1398.93 cm^{-1} due to –OH bending, 1294.83 cm^{-1} due to C–N stretching, and 1216.40 cm^{-1} due to C–O stretching. The FTIR spectra of solid dispersion also exhibited the characteristic peaks of febuxostat, albeit with a slight shift in their positions. This shift suggests a slight broadening of the peaks, which can be attributed to the formation of stable hydrogen bonds. These hydrogen bonds are respon-
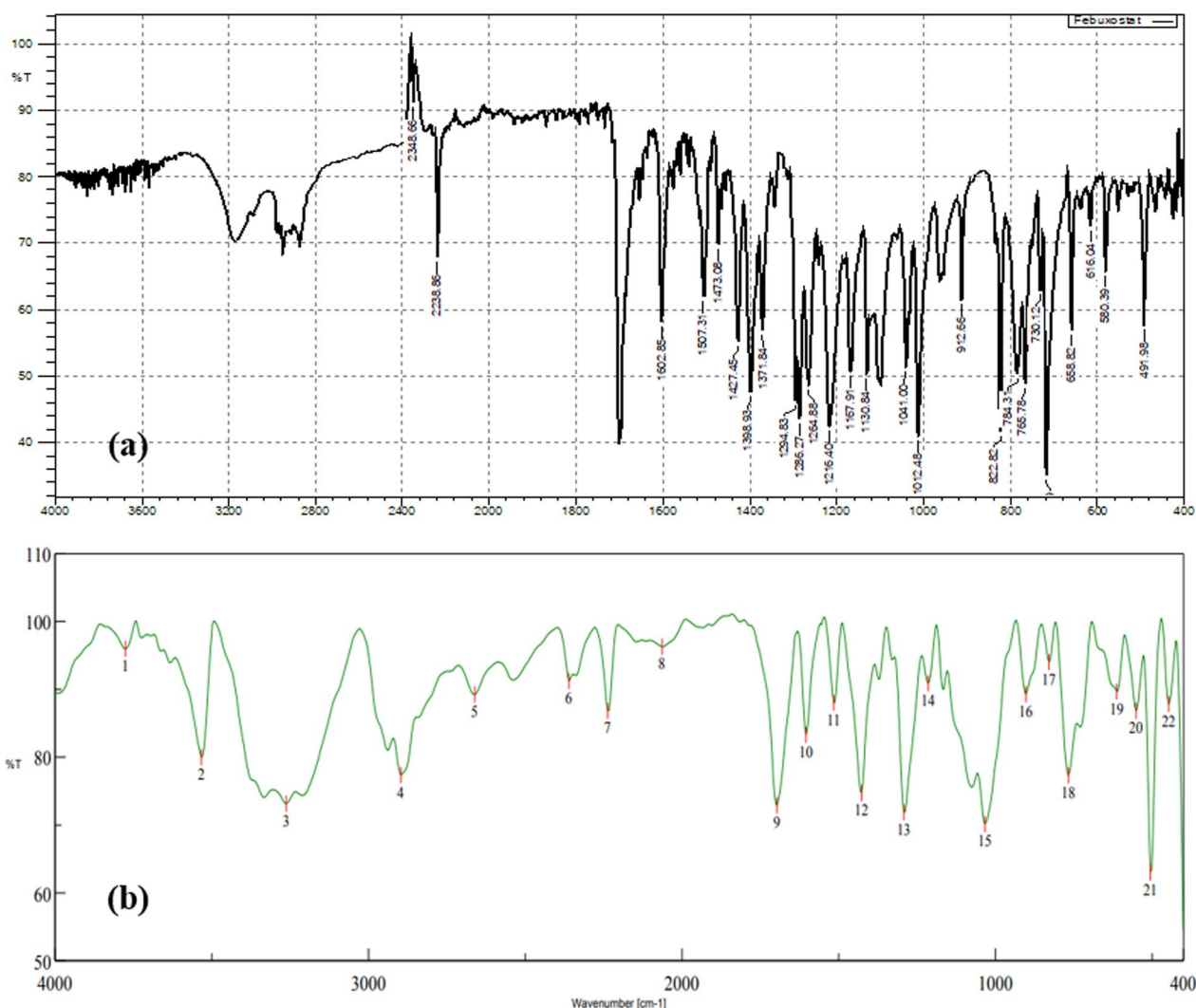
Fig. 2 a FTIR spectra of pure drug **b** FTIR spectra of solid dispersion

sible for the formation of a dispersion between the drug and soluplus, consequently enhancing the solubility of febuxostat. The phenomenon of peak disappearance was observed in this study, which can be attributed to the amorphous nature of the drug under investigation. The FTIR spectra depicted in Fig. 2 illustrate the distinct spectral characteristics of the pure drug and solid dispersion. Thus, the FTIR study revealed that polymer does not interact with the drug and is suitable for the development of formulation.

Differential scanning calorimetry DSC thermogram of crystalline febuxostat showed single sharp endothermic melting peak at 232 °C (Fig. 3a). DSC spectra of solid dispersion showed shifting and reduction of peak (Fig. 3b) which suggests that the drug remains in the amorphous state for a longer duration. The conversion of drug from

crystalline to amorphous leads to enhancement of dissolution rate of drug. Thus, it suggests that drug excipient interaction was not observed.

In vitro dissolution rate studies on solid dispersions Phase solubility data concluded maximum solubility enhancement in 1:2 ratio of solid dispersion in acetate buffer pH 4.5 and phosphate buffer pH 7.4. For confirmation, in vitro dissolution rate studies were performed which is expressed in Fig. 4. 1:2 ratio achieved faster drug release in acetate buffer pH 4.5 and phosphate buffer pH 6.8 due to dispersion formation between drug and soluplus. Therefore, we may conclude that 1:2 ratio of solid dispersion was optimized for preparation of IR and SR formulation. Enhancement of dissolution was due to lack of crystalline state, particle size reduction, and adsorption of soluplus on the surface of drug.
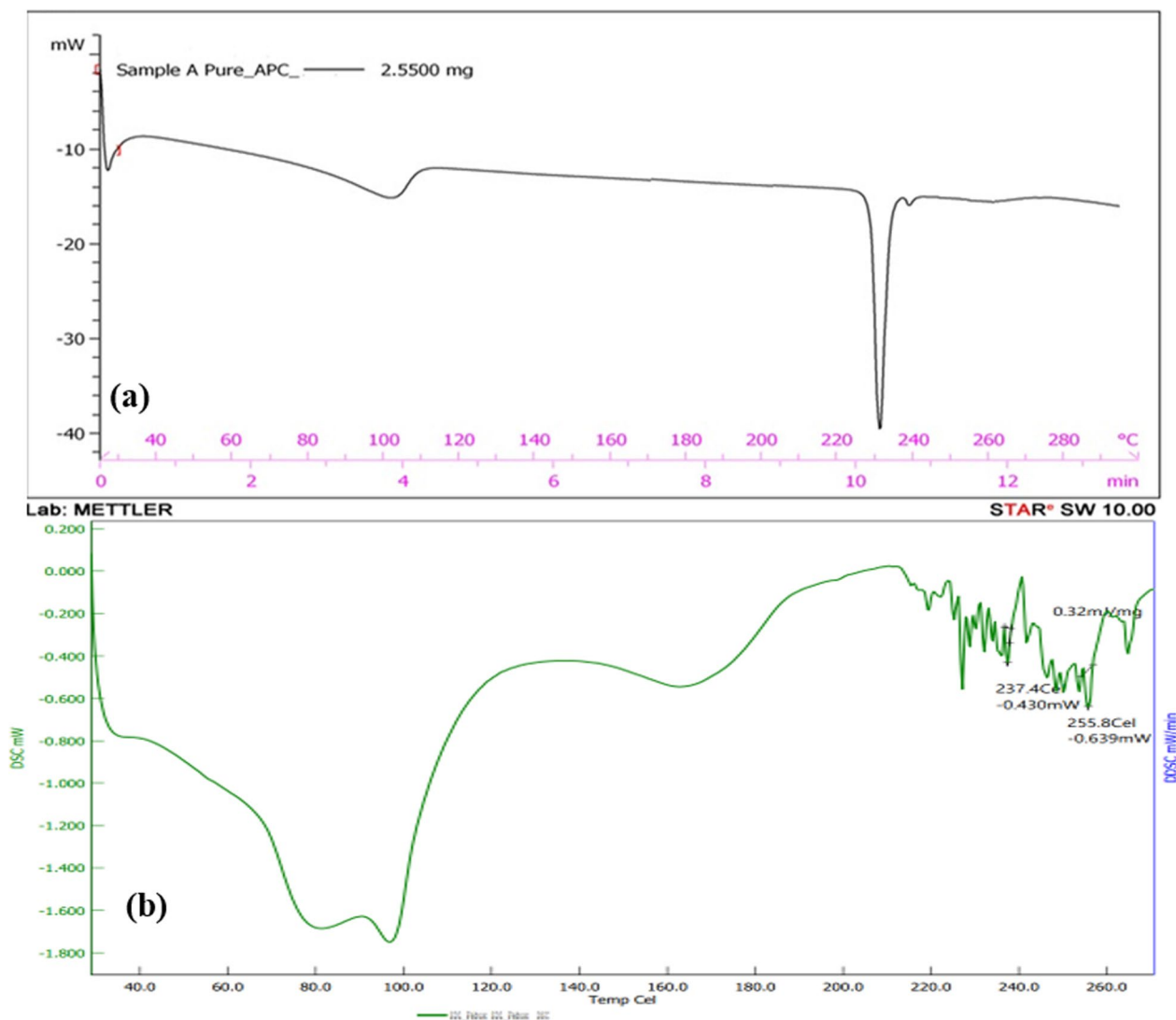
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Fig. 3 **a** DSC thermogram of pure drug **b** DSC thermogram of solid dispersion

Development of pulsatile drug delivery for febuxostat
Coating of capsule body and optimization
For the preparation of Pulsincap, non-soluble hard gelatin capsule of '000' size was chosen. Ethyl cellulose, a polymer with hydrophobic properties, demonstrates exceptional capability in generating films that are highly resistant to water solubility. Dibutyl phthalate, which acts as plasticizer, was incorporated to provide flexibility, mechanical strength, and thermo plasticity. Therefore, coating of capsule body was done using 10%w/v ethyl cellulose in methanol with 0.5% dibutyl phthalate [17]. The coated capsules were subsequently subjected to an integrity assessment by immersing them in an acetate buffer with a pH of 4.5 for a duration of 2 h. This was followed by a 12-h immersion in a phosphate buffer with a pH of 7.4, during which the integrity of the coated capsules was evaluated. The integrity of the single coated capsule body was observed to be compromised within a time frame of 6 h. However, double-coated capsule body maintained integrity for approximately 12 h, which was found sufficient for desired drug release in chronotherapeutic manner. Thus, optimized number of coatings was found to be 2.

Evaluation of prepared SR and IR tablets
Prepared SR and IR tablets were evaluated for the precompression parameters and exhibited good to passable flow properties. Hardness of SR tablet was maintained 6 kg/cm^2, whereas hardness of IR was maintained 4 kg/cm^2 which can aid faster disintegration without affecting its friability limits (< 1%). The tablets under investigation
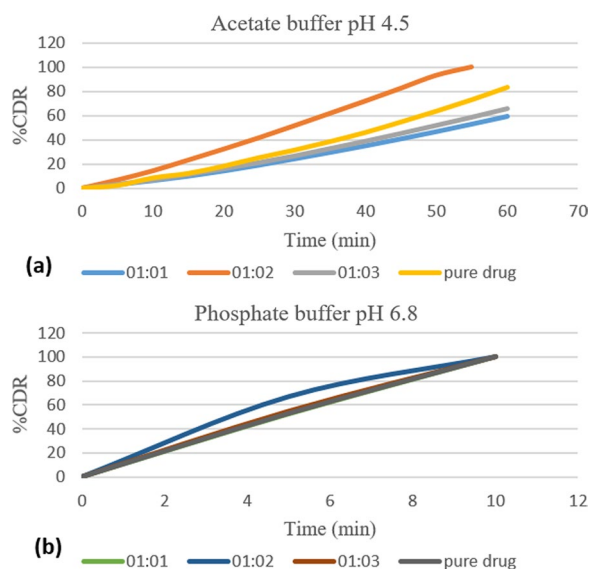
Fig. 4 In vitro dissolution of solid dispersion in: **a** acetate buffer pH 4.5 **b** phosphate buffer pH 6.8

were observed to possess a flat, circular shape, with a thickness of 4 mm for IR tablets and 6.5 mm for SR tablets. Furthermore, the tablets exhibited a diameter of 5 mm. The tablets were observed to exhibit consistent weight, displaying an acceptable level of variation in accordance with the specifications outlined in the IP. Drug content was found between 96.98 and 99.79%. Disintegration time of IR tablets were performed in acetate

buffer pH 4.5 and phosphate buffer pH 6.8. Tablet containing crospovidone as superdisintegrant achieved faster disintegration in both media (< 5 min) as compared to tablet containing sodium starch glycolate (< 10 min).

In vitro drug release study of prepared SR tablets was performed and compared with marketed SR tablet in phosphate buffer pH 6.8 and 7.4 for 6 h. S1 gave optimum drug release in pH 6.8 and 7.4; S2 retards the drug release in pH 6.8 but showed faster drug release in pH 7.4 due to higher viscosity grade of HPMC; S3 achieved slower drug release in pH 6.8 as compared to S1, whereas S4 gave immediate release in both pH due to presence of water-soluble excipient—lactose. Therefore, S1 was optimized for achieving desired sustained release effect and gave sustained effect for longer time as compared to marketed SR (Fig. 5). In vitro drug release study of prepared IR tablet was performed and compared with marketed IR tablet in acetate buffer pH 4.5 and phosphate buffer pH 6.8. Having better disintegration time, R1 gave faster drug release in pH 4.5 and 6.8 as compared to R2. Therefore, R1 was optimized for achieving desired immediate release effect and gave almost equivalent drug release as compared to marketed IR (Fig. 5).

Evaluation of polymers for erodible plug
Screening of different polymers was carried out for preparation of erodible plug. Pre-compression parameters were performed and showed good flow properties.
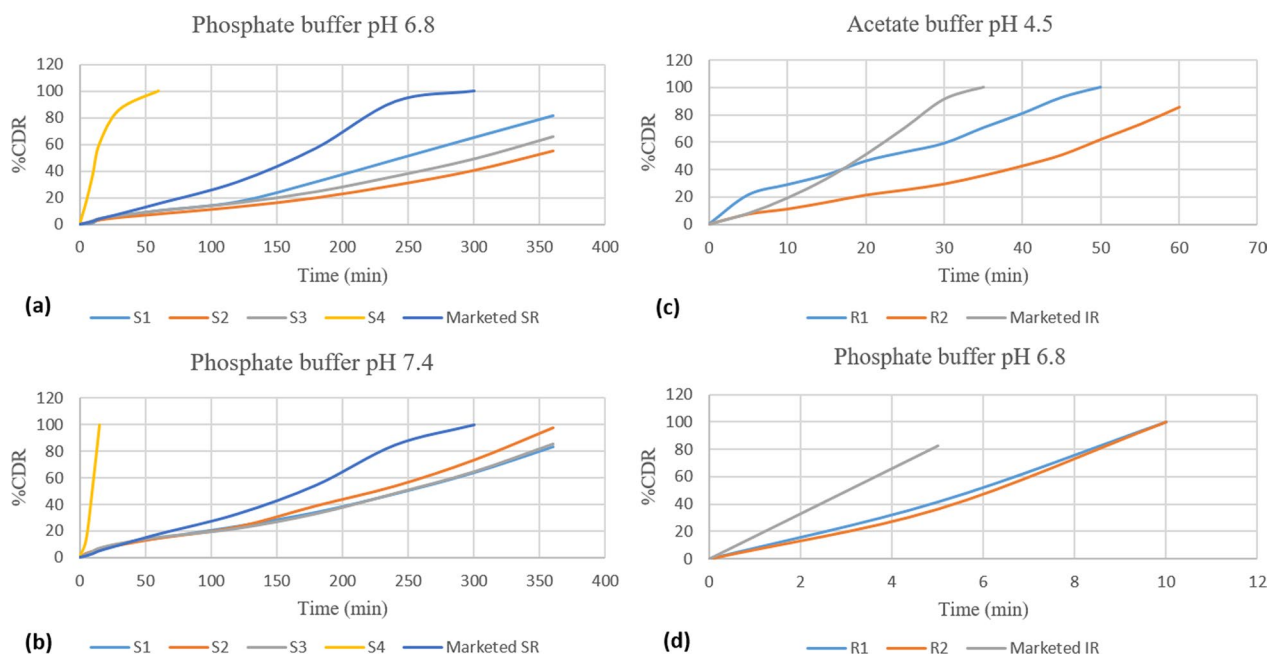

Fig. 5 In vitro dissolution of preliminary batches of: **a** SR in phosphate buffer pH 6.8 **b** SR in phosphate buffer pH 7.4 **c** IR in acetate buffer pH 4.5 **d** IR in phosphate buffer pH 6.8

Guar gum possesses highest swelling capacity but lacked binding property. So, the plug prepared from guar gum had minimum hardness and maximum friability. HPMC K15M possesses excellent binding property. Hence, HPMC was used along with guar gum to maintain the plug's integrity. Aloe vera possess swelling capacity and it also gives therapeutic effect in treatment of gout. In order to achieve therapeutic levels during lag time, aloe vera (powder) was used in formulating erodible plug. Erodible plug prepared from mixture of guar gum, HPMC K15M, and aloe vera remained intact with a lag time of 6 h, 62% swelling index, and % erosion was found to be 43%. Therefore, mixture of aloe vera, guar gum, and HPMC K15M was screened out for preparation of erodible plug.

Optimization of erodible plug

For 3^2 factorial design, a total of nine experiments were performed for two factors at three levels each. All the nine formulations were evaluated for pre- and post-compression studies. The flow property was observed to be good. Weight variation was within the range as per IP specifications. Friability was within the limits (<1%). % erosion was found between 35 and 45%.

3^2 factorial design was used to optimize the concentration level of independent factors and its interaction with the dependent factors to achieve maximum swelling index in 6 h with optimum hardness to retain the shape and desired lag time for the pulsatile delivery. As shown in Table 3, % swelling in 6 h was found between 60 and 75% with hardness 3.5–6.5 kg/cm^2 and a lag time of 8–12 h.

All the three responses were fitted to different statistic models. Responses Y_1 and Y_2 confirmed highest adjusted and predicted R^2 values in linear model, whereas

Table 4 Regression statistical analysis for the observed responses of 3^2 full factorial design

	Response Y_1	Response Y_2	Response Y_3
R^2	0.8314	0.8794	0.9937
Adjusted R^2	0.7751	0.8392	0.9831
Predicted R^2	0.6176	0.7006	0.9331
Adeq precision	10.6754	13.1711	28.0558
PRESS value	134.69	1.17	0.8568
F value	14.79	21.88	94.20
p value	0.0048	0.0018	0.0017
Coefficients			
β_0	+67.17	+5.12	+9.41
β_1 (X_1)	−5.80	+0.5833	−1.35
β_2 (X_2)	+3.90	+0.4833	−0.5333
β_{12} (X_1X_2)	–	–	−0.1500
β_3 (X_1^2)	–	–	−0.0167
β_4 (X_2^2)	–	–	+0.0333

response Y_3 confirmed highest values in quadratic model to study the interaction effect between selected variable and response. Adequate precision was >4 in all the three responses. C.V. % was found to be less than 10 which was desirable. P value was <0.05. Therefore, reliability of model was confirmed. Regression statistical analysis of the three responses are represented in Table 4.

2D and 3D plots were drawn as shown in Fig. 6 to estimate the effect of independent variable on each response. Figure 6a represents the effect on swelling index. It indicates that on increasing concentration of HPMC K15M, swelling index decreases. But, mixture of guar gum and aloe vera showed positive effect on swelling index. Figure 6b shows the effect on hardness. It indicates that

Table 3 Experimental runs projected for 3^2 full factorial design and their observed responses

| Batches	Coded value		Uncoded value		Y_1 % Swelling index (%) $n=3$, (±S.D.)	Y_2 Hardness (kg/cm^2) $n=3$, (±S.D.)	Y_3 Lag time (h) $n=3$, (±S.D.)
	X_1	X_2	X_1	X_2			
B1	−1	+1	80	100	69.3±0.14	3.9±0.002	11.2±0.003
B2	0	+1	90	100	62.3±0.035	5.1±0.003	9.9±0.002
B3	+1	+1	100	100	74.81±0.213	4.9±0.004	10.3±0.003
B4	0	0	90	90	73.2±0.059	5.6±0.001	9.1±0.004
B5	−1	0	80	90	60.3±0.0158	4.8±0.003	8.8±0.02
B6	+1	0	100	90	55.39±0.078	5.8±0.008	8.1±0.004
B7	+1	−1	100	80	67.3±0.054	6.2±0.009	7.3±0.007
B8	0	−1	90	80	68.3±0.03	5.3±0.004	9.3±0.001
B9	−1	−1	80	80	73.65±0.024	4.5±0.009	10.8±0.002
V1	–	–	91.71	101.56	72.53±0.054	5.9±0.001	8.4±0.02
V2	–	–	89.34	94.71	66.42±0.079	4.8±0.003	9±0.003
V3	–	–	95.44	87.44	62.98±0.458	5.0±0.006	8.9±0.001
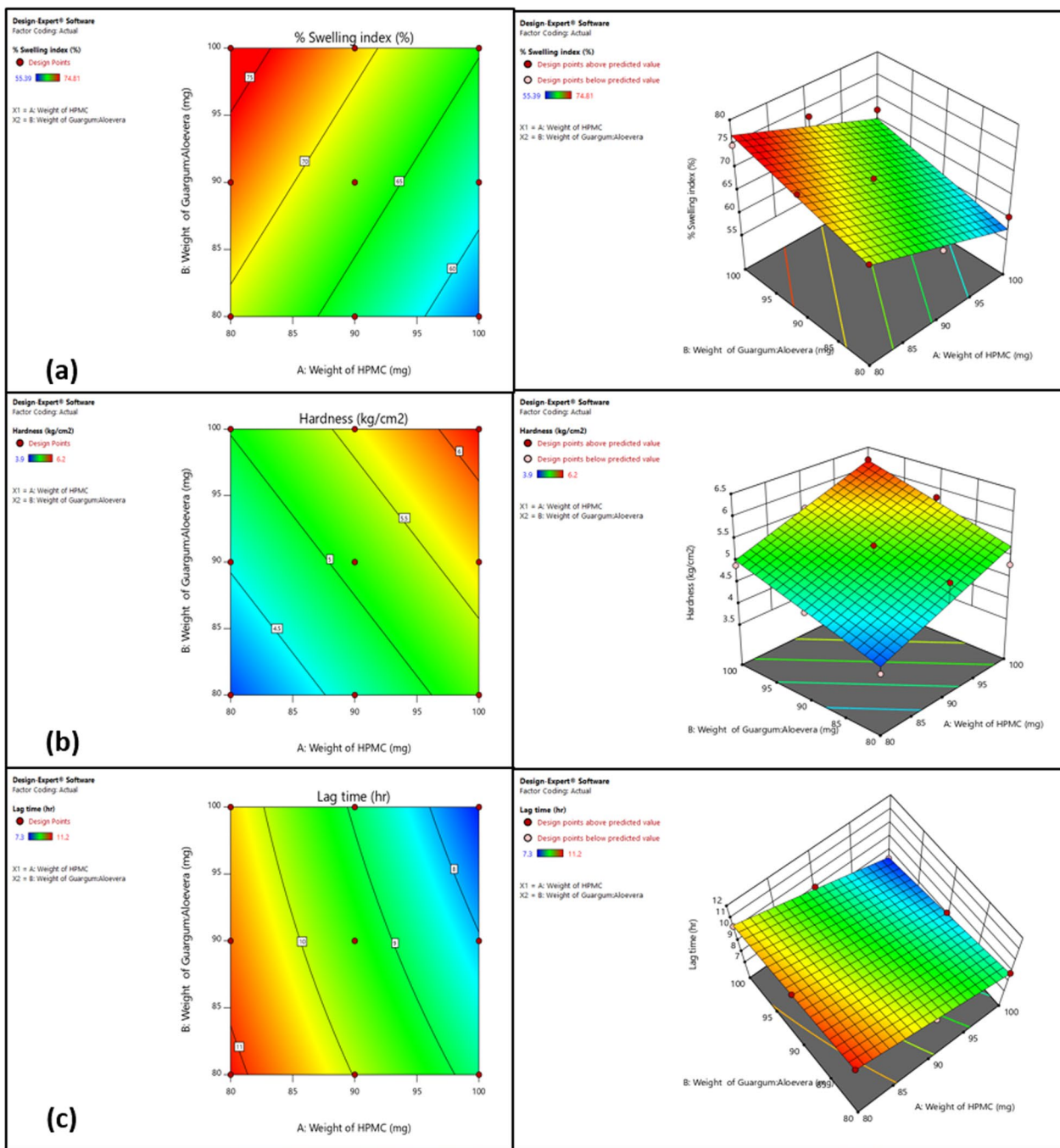
Fig. 6 2D and 3D contour plot for: **a** Y_1 response **b** Y_2 response **c** Y_3 response

on increasing concentration of HPMC K15M, hardness increases. But, mixture of guar gum and aloe vera showed negative effect on hardness. Figure 6c represents effect on lag time. It indicates that on increasing concentration of HPMC K15M, lag time decreases. But, mixture of guar gum and aloe vera showed positive effect on lag time.

Final equations in terms of coded and uncoded factors:

$$\% \text{ swelling index} = +67.17 - 5.80A + 3.90B$$

$$\% \text{ swelling index} = +84.21222 - 0.579500 * \text{Weight of HPMC} + 0.390167$$
$$* \text{Weight of Guar gum} : \text{Aloe vera}$$

$$\text{Hardness} = +5.12 + 0.583A + 0.483B$$

$$\text{Hardness} = -4.47778 + 0.058333 * \text{Weight of HPMC} + 0.048333$$
$$* \text{Weight of Guar gum} : \text{Aloe vera}$$

$$\text{Lag time} = +9.41 - 1.35A - 0.53B - 0.15AB - 0.016A^2 + 0.033B^2$$

$$\text{Lag time} = +15.56111 + 0.030000 * \text{Weight of HPMC} + 0.021667$$
$$* \text{Weight of Guar gum} : \text{Aloe vera}$$
$$- 0.001500 * \text{Weight of HPMC} * \text{Weight of Guar gum} : \text{Aloe vera}$$
$$- 0.000167 * \text{Weight of HPMC}^2 + 0.000333$$
$$+ \text{Weight of Guar gum} : \text{Aloe vera}^2$$

Response 1 was set with 55–75% goal, response 2 was set with 5–6.5 kg/cm^2 goal, whereas response 3 was targeted for 8–10 h. In conclusion, 91.71 mg HPMC K15M along with 101.56 mg mixture of guar gum and aloe vera can accomplish prerequisites of optimum formulation and can achieve swelling index, hardness, and lag time within the desired goals. Actual vs. predicted graphs of all the responses are included in Fig. 7.

Validation of experimental design

A concentration-optimized formulation was prepared and evaluated for in vitro dissolution investigations. The result of calculating relative error based on predicted and experimental values was found to be within the acceptable range (10%). Thus, the design's precision was affirmed. Overlay plot is shown in Fig. 8.

Fabrication of optimized formulation

The optimized formulation was prepared and evaluated for in vitro drug release. SR tablet was filled into coated capsule followed by the erodible plug. The IR tablet was placed inside the water-soluble cap, and the cap was used to encapsulate the body. The experiment begins with the water-soluble cap dissolving within 5–7 min, followed by the discharge of the IR tablet. The IR tablet's

drug release generated the first pulse within one hour. The second pulse was generated after a delay of 7–8 h due to the release of the medication from the SR tablet (Fig. 9). > 90% drug release from both tablets indicates therapeutic efficacy of developed system.

Stability studies of optimized formulation

Stability studies were performed for the optimized pulsincap. The capsule was stored at the required condition and % cumulative drug release at 1 h and 8 h was taken each week. The formulation was evaluated for degradation. Data are depicted in Table 5. It was concluded that the formulation was stable and degradation was not found.

Discussion

In the present investigation, we have developed chronotherapeutic system of febuxostat. Initially, the possible drug–polymer interaction was accessed through FTIR and DSC studies. Results revealed that the drug–polymer combination was compatible and the formulation development was possible. Solid dispersion was prepared to enhance the solubility of drug. Soluplus was used as the carrier for dispersion using physical mixing process. 1:1 ratio of drug/soluplus was not found optimum as the equal amount of drug and polymer might lead to poor drug dispersion within the matrix. It may result in drug-rich or polymer-rich regions within the dispersion matrix. In 1:2 ratios, excess polymer might help in better dispersing the drug particles within the matrix, thereby
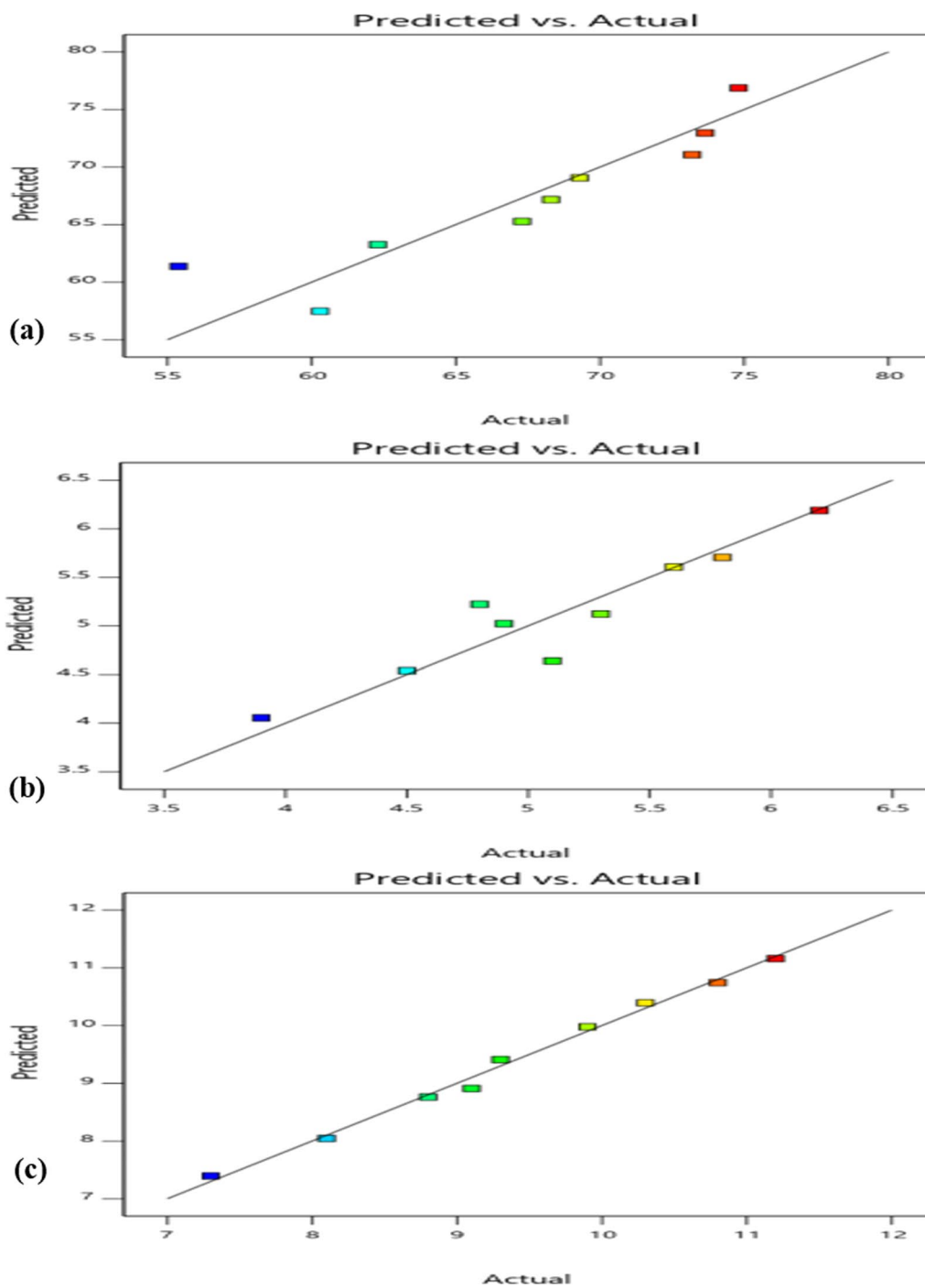
Fig. 7 Actual vs predicted graphs of **a** Y1 response **b** Y2 response **c** Y3 response
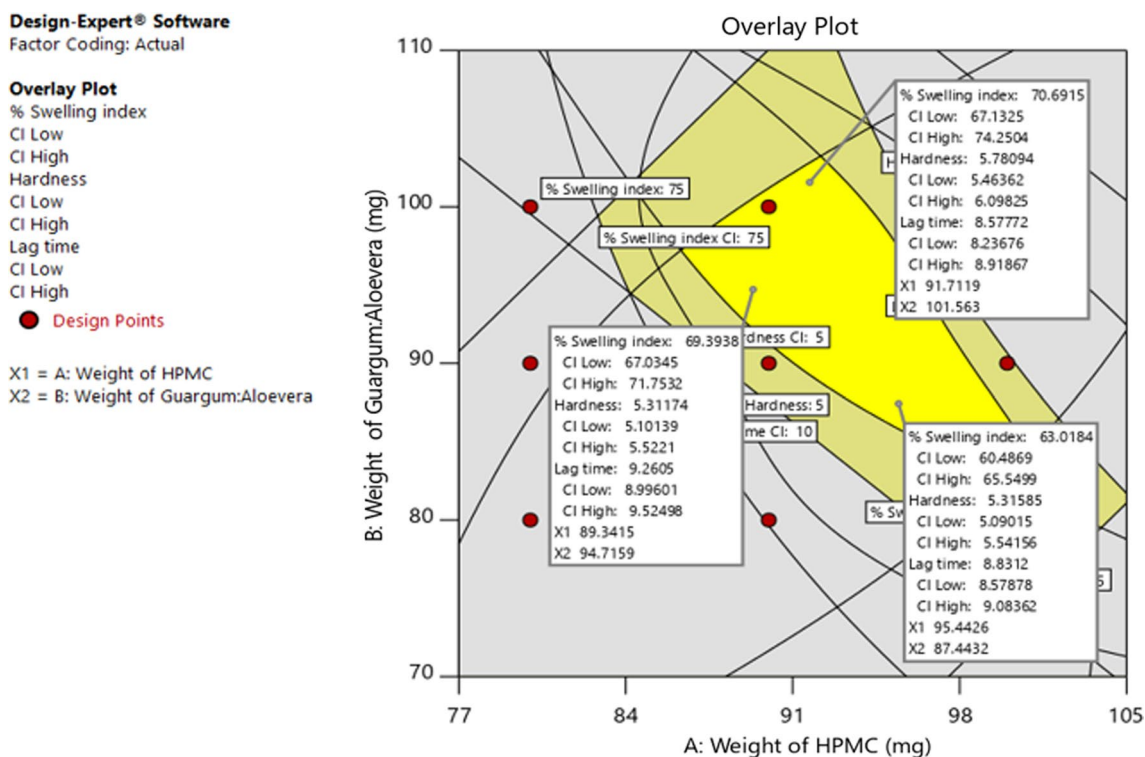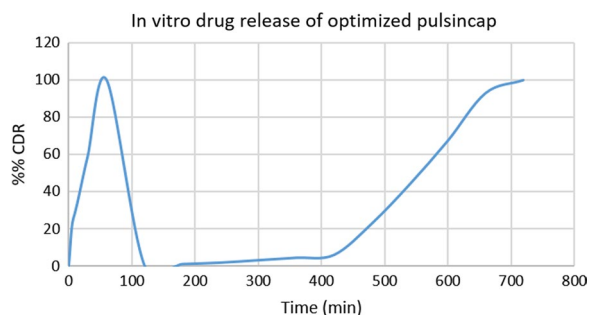
Fig. 8 Overlay plot

Fig. 9 In vitro drug release of optimized pulsincap

enhancing the solubility. In 1:3 ratios, higher proportions of polymer may result in aggregation or clustering of drug particles, leading to lower solubility. All the prepared powders for solid dispersion showed better flow properties due to decrease in cohesion and particle size reduction by physical mixing. 1:2 ratio of drug/soluplus showed better drug release in acetate buffer pH 4.5 and phosphate buffer pH 6.8 because high polymer content leads to better interaction with the drug molecules. '000' size capsule was chosen for the development of pulsincap. Body of the capsule was coated with 10% w/v ethyl

Table 5 Stability studies of optimized Pulsincap

Time (weeks)	Before		After	
	% CDR at 1 h	% CDR at 8 h	% CDR at 1 h	% CDR at 8 h
1	100 ± 0.002% IR	22.66 ± 0.015% SR	100 ± 0.001% IR	22.13 ± 0.023% SR
2			100 ± 0.003% IR	21.76 ± 0.01% SR
3			100 ± 0.001% IR	22.02 ± 0.076% SR
4			100 ± 0.001% IR	21.98 ± 0.045% SR

cellulose in methanol and 0.5% dibutyl phthalate and the optimized number of coatings were found to be 2. All the prepared IR and SR tablet powder blends were evaluated for micromeritic properties. All the blends showed good to passable flow property due to the dry mixing method. S1 had the best flow property compared to S2–S4 because of low viscosity HPMC grade. S2 was formulated with high viscosity grade of HPMC, whereas S3 was prepared by mixing low and high viscosity grade of HPMC. S4 had the lactose monohydrate which itself has the poor flow property, leading to decreased flow property of formulation [23]. R1 was prepared by crospovidone which had better flow property compared to R2 prepared from sodium starch glycolate. Crospovidone swells without gelling which is an advantageous property against sodium starch glycolate as gelling can delay dissolution process [24]. The hardness of immediate release tablets was kept constant, i.e., 4 kg/cm^2. As per the reported literature, tablet hardness had direct relationship with friability. Increase in hardness decreases the friability. All the formulation had friability within the limit of < 1%. Weight of all the IR tablets was close proximity to the actual value of 100 mg. The disintegration time of R1 was faster compared to R2. R1 disintegrated in < 5 min and also achieved faster drug release, whereas R2 disintegrated in < 10 min with poor drug release compared to R1. As mentioned previously, due to the mechanism of sodium starch glycolate, it shows poor release compared to crospovidone. The hardness of sustained release tablets was kept constant, i.e., 6 kg/cm^2. Friability was within the range of < 1%. Weight of all the SR tablets were close proximity to the actual value of 150 mg. S1 showed drug release in a controlled and sustained manner within the desired time period. S1 achieved 81% drug release at the end of 6th h because of presence of low viscosity grade of HPMC while S2 achieved 55% release due to higher viscosity grade and S3 achieved 66% release due to combination of low and high viscosity grade of HPMC. Higher viscosity polymers form thick and viscous layers of gel upon contact with water, preventing diffusion of drug molecules and water uptake. S4 achieved 100% drug release in 1 h because lactose leads to quick disintegration and drug release. Polymers for erodible plug was evaluated. Combination of HPMC K15M, guar gum, and aloe vera was chosen. HPMC K15M served as a binding agent, while guar gum and aloe vera possess swelling property. Aloe vera also possess therapeutic efficacy in treatment of gout. This combination remained intact for 6 h with desired swelling index.

For the optimization of erodible plug, 3^2 full factorial design was used. Concentration of HPMC K15M and amount of aloe vera, guar gum mixture were taken as independent variables. Based on the design, total nine formulation combinations (B1–B9) were made and evaluated for micromeritic properties. The value of coefficient of correlation (r^2) for the best fit model 0.8314–0.9937 is observed. The effect of variables on % swelling, hardness, and lag time was investigated through polynomial equation and response curves. The factors affecting disintegration time were concentration of HPMC K15M and amount of aloe vera, guar gum mixture. The predicted % swelling values obtained by model using above equation were compared with observed values. < 5% error ascertained good model predictability. The amount of aloe vera, guar gum mixture had negligible effect on % swelling. But, concentration of HPMC K15M had a negative effect. Guar gum and aloe vera possess swelling property. Therefore, it leads to greater swelling index. Concentration of HPMC K15M had negligible effect on hardness, but guar gum, aloe vera mixture had a negative effect. HPMC K15M, being a binder, provides good compactness to the formulation. The amount of aloe vera, guar gum mixture had negligible effect on lag time, while concentration of HPMC K15M had a negative effect. Guar gum and aloe vera swell up to a certain limit and then explode out of the capsule. The significance of model was evaluated through ANOVA. ANOVA and PRESS value suggested that the model was fit for evaluation. The response surface and contour plots suggested the concentration of HPMC K15M to be 91.71 mg and amount of aloe vera, guar gum mixture to be 101.56 mg. The predicted value of % swelling was 70.69%; hardness was 5.78 kg/cm^2 with a lag time of 8.57 h. Finally, the capsule was filled with SR in the body of capsule, erodible plug in between the cap and body of capsule and IR in the cap of the body were evaluated. Thus, the formulation met the requirement of providing immediate release in 1st h, followed by a lag time and sustained release for a duration of 12 h.

Conclusion

In the present study, an attempt had been made to enhance solubility of febuxostat by solid dispersion technique and formulate pulsincap for treatment of gout. SR and IR tablets were optimized by in vitro drug release studies. Erodible plug was optimized by applying the 3^2 full factorial design as the optimum parameters for the preparation of erodible plug having desired qualities including % swelling index, hardness, and lag time. Thus, we conclude that the optimized batch achieved drug release at the morning time when the uric acid levels achieve peak serum concentration.

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Abbreviation

ANOVA	Analysis of variance
CR	Controlled release
CV	Coefficient of variation
DSC	Differential scanning calorimetry
FTIR	Fourier transform infrared spectroscopy
HPMC K15M	Hydroxy propyl methyl cellulose K15M
IR	Immediate release
MLR	Multiple regression analysis
PRESS	Predicted residual sum of square
SR	Sustained release
SUA	Serum uric acid
UV–VIS Spectrophotometer	Ultraviolet–visible spectrophotometer
XOI	Xanthine oxidase inhibitor

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Author contributions
KP contributed to investigation, software, validation, formal analysis, and writing original draft. VT contributed to conceptualization, methodology, supervision, and project administration. AJ and CS contributed to software, validation, and formal analysis. SD and HR contributed to review and editing the draft.

Availability of data and materials
All the relevant data are provided in the manuscript. If any additional data are required, it will be available upon request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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