RESEARCH ARTICLE

Formulation and Optimization of Febuxostat-Loaded Nanosponges for Oral Delivery*: In-Vitro* Characterization and Evaluation

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ABSTRACT

Over the past decade, there has been a significant rise in innovative therapy approaches for various rheumatic conditions, including gout. Gout is a severe manifestation of uric acid imbalance. Recent revelations into the biology of hyperuricemia and both acute and chronic gouty arthritis enhance the comprehension of the condition. In recent years, two new medicinal drugs have been licensed for gout treatment, one of which is febuxostat, a nonpurine selective xanthine oxidase inhibitor. Notwithstanding the numerous benefits, there may be specific problems associated with the drug distribution and other facets of Febuxostat. Nanotechnology has demonstrated considerable efficacy in addressing these difficulties. It offers a novel healthcare paradigm and has the potential to rejuvenate current therapeutic goods. The present study seeks to formulate, optimize, and further develop nanosponges utilizing ethyl cellulose as a polymer through the solvent diffusion method. The nanosponges were subsequently compressed into tablets using the direct compression method and were further assessed.

This work aims to formulate and assess Febuxostat-loaded nanoparticles utilizing Ethyl Cellulose as a polymer, evaluate physicochemical properties, and create a tablet dosage form containing the nanosponges.

Keywords: Gout, Nanosponges, Febuxostat, Tablet, Polymer, Solvent Diffusion Method, Ethyl Cellulose.

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INTRODUCTION

Gout is a common rheumatological disorder caused by an imbalance in uric acid levels as well as its excretion. It is characterized by hyperuricemia along with the presence of traces of monosodium urate.[1] Cardiovascular diseases are common comorbidities with gout, including obesity, dyslipidemia, hypertension, and insulin resistance.[2] Because estrogen has a uricosuric impact, gout is more common in men and less so in women. However, gout appears to become more common after menopause.[3] Despite the use of various medications, rebound gout attacks can occur after abrupt discontinuation of treatment. Febuxostat (FXT) is a xanthine oxidoreductase inhibitor from BCS class II that has a high lipophilicity but is thought to work better than allopurinol. It has a protein binding rate of 99%, a plasma half-life of 5-7 hours, and a bioavailability of 45-50%. Its bio-availability is restricted by its low water solubility and the enzymes that break it down.[4]

Febuxostat, administered orally, suppresses xanthine oxidase, a crucial enzyme in the transformation of hypoxanthine and xanthine to uric acid, therefore reducing uric acid production and serum levels. Gout is the most prevalent uric acid-related illness.[5] When uric acid builds up in a joint, it causes a form of arthritis. Both the US Food and Drug Administration and the European Medicines Agency gave their stamp of approval for its marketing in 2008 and 2009, respectively. A normal oral dosage of 40 to 80 mg is required because to its short biological half-life, which increases the frequency of dosing.[6,7]

Having a pKa value of 3.08 and being a weak acid, Febuxostat is a compound with low solubility and high permeability. Because of the first-pass effect, oral bioavailability is impaired, and medication concentration drops 38–39% when food is present, limiting clinical applicability.[8] Innovative formulations for managing gout are needed, including liposomes, nanoemulsions, self-microemulsions, nanocrystals, neosomal gel, and nanosuspension. However, these formulations have drawbacks such as low entrapment efficiency, leakage problems, and instability.[9-11] Liposomes face issues like scale-up, manufacturing expense, and storage stability. Clinical applications are limited by issues like sedimentation and compaction problems, shorter shelf life, aggregation, drug leakage, instability, and vesicle fusion of neosomal gel.[12,13] A fresh strategy is needed to address these challenges. The release of drugs can be more precisely controlled using nanotechnological methods, such as nanosponges and nanocapsules.[14] Medication can be more precisely and reliably delivered with the help of nanospheres, which are tiny, spherical, and porous delivery

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Table 1: Investigating ranges of variable for corn starch and povidone

Sr. No.	Factor	Low level	High level
A	Corn starch	102	108
B	Povidone	10	14

systems. Perfect for sustained-release formulations, they have a number of benefits including fewer side effects, more dosage forms, less irritations, and better aesthetics.[15-17]

A variety of oral formulations of Febuxostat, such as solid dispersions, nanosuspensions, microspheres, and the formation of choline salt, were formulated to improve the bioavailability of Febuxostat.[18,19] This work focused on the encapsulation of Febuxostat in nanosponges, followed by their further processing in tablets using β-Cyclodextrin (β-CD) and dichloromethane for prolonging the release and promoting the bioavailability of the drug.

Nanosponges can be made using a variety of techniques, such as the solvent method, the cross-linking of β cyclodextrins, the emulsion solvent diffusion method, and ultrasonic assisted synthesis. Particle size, medication loading, entrapment efficiency, and release profile are the parameters that nanosponges are tested for. Addtionally, FTIR, PXRD, and SEM are generally used for structural analysis.

Therefore, this work set out to do just that—create and assess EC-based sustained-release formulations of FEB-loaded NS. In vitro drug release rate assessment and testing of prepared formulations were conducted for a number of physicochemical characteristics. The last step was to test the formulation qualities of a tablet dosage form that contained NS.

EXPERIMENTAL

MATERIALS

Feboxostat was provided by Excel Industries Limited. Ethyl cellulose (EC), dichloromethane (DCM), Methanol was of analytical grade were purchased from S. D. Fine chemicals.

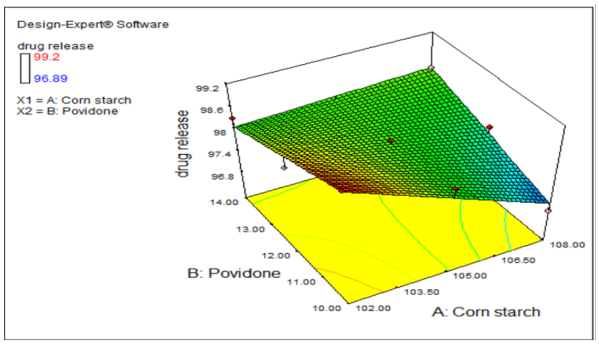
METHODS

Production of FEB-loaded NS

The polymer was mixed with a suitable solvent—more especially, a polar aprotic solvent dimethylformamide (DMF) for the production of the nanosponges. The resultant combination was then added in excess to cross-linker. Over four to five hours, the reaction was conducted at 10°C temperature to the solvent's reflux temperature. It was then allowed to cool to the surrounding temperature once it was finished, then adding a lot of bidistilled water precipitated the result. Vacuum filtration gathered the precipitated product, which was then purified over many Soxhlet runs running ethanol. To get a homogenous powder, the pure product was processed using a mechanical mill then dried under a vacuum. This ratio was chosen for additional research since among the evaluated ratios, a 1:2 polymer-to-cross-linker ratio produced more products and showed a spherical shape.

Drug Loading into Nanosponges

Drug loading was conducted via a mechanical stirrer.



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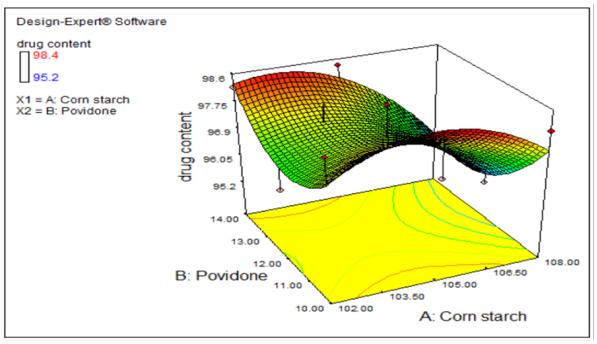

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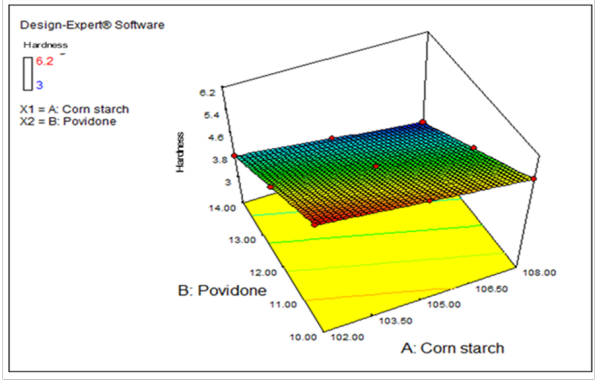

(C)

Figure 1: (A) 3D Surface Plot of % Drug Release of Febuxostat with Respect to corn starch and povidone; (B) 3D Surface Plot of % Drug content of Febuxostat with respect to corn starch and povidone; (C) 3D Surface Plot of Hardness of Indomethacin with Respect to Xanthan gum &PVP K-30 Desirability plot

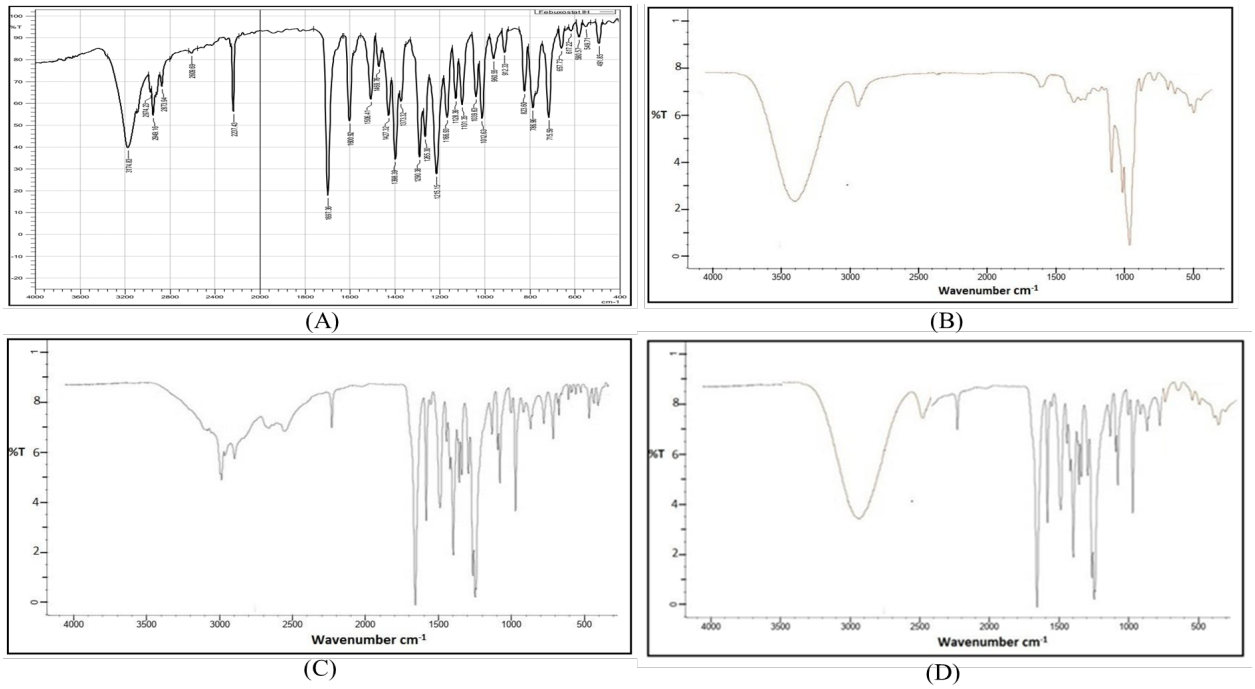

Figure 2: (A) FT-IR spectra of Pure Febuxostat; (B) FT-IR spectra of β-cyclodextrin ;(C) FT-IR spectra of Febuxostat and β-cyclodextrin (Physical mixture); (D) FT-IR spectra of Febuxostat nanosponges

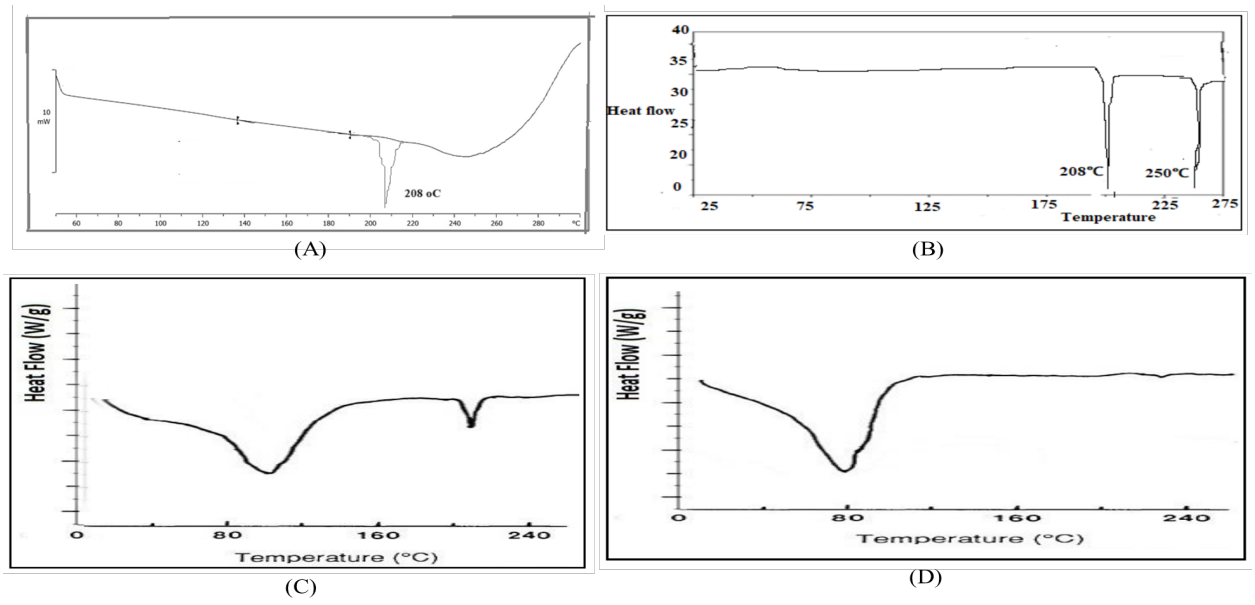

Figure 3: (A) DSC Thermogram of Febuxostat; (B) DSC Thermogram of Febuxostat Nanosponges; (C) DSC Thermogram of Physical mixture of Drug and Polymer (1:1); (D) DSC Thermogram of β-Cyclodextrin

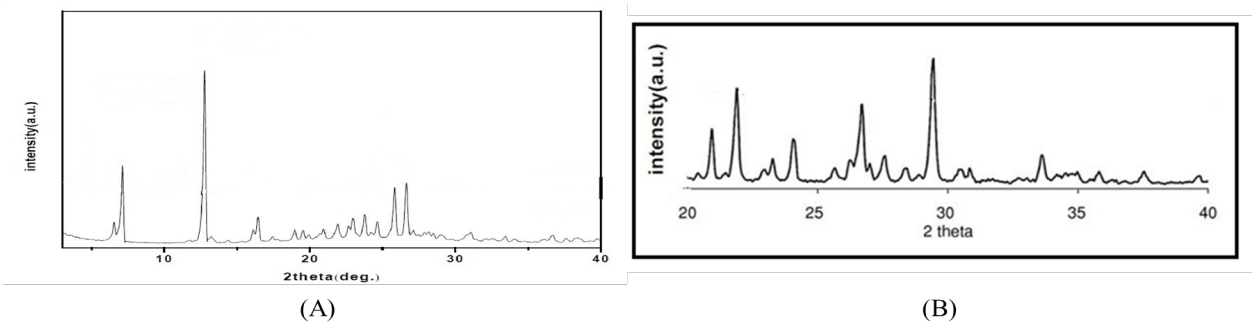

Figure 4: (A) XRD patterns of Febuxostat; (B) XRD patterns of Febuxostat nanosponges

Table 2: Ingredients for tablet compression

Ingredients	Quantity in batch (mg)					
	F1	F2	F3	F4	F5	F6
Febuxostat nanosponges	200	200	200	200	200	200
Silica colloidal anhydrous	2	2	2	2	2	2
Corn starch (starch 1500)	102	105	108	102	105	108
Povidone- povidone k,30 (binder)	10	10	10	12	12	12
Micro crystalline cellulose (avicel pH 102)	45	45	45	45	45	45
Magnesium stearate USP/NF (lubricant)	3.5	3.5	3.5	3.5	3.5	3.5
Isopropyl alcohol IPA99% (solvent)	Quantity Sufficient					

Table 3: Process parameter for preparation of Placebo Nanosponges

Ratio	1:1	1:2	1:3	1:4	1:5
DMF+ β-cyclodextrin (gm.)	1	1	1	1	1
Dichloromethane (ml)	0.75	1.50	2.25	3.00	3.75

Table 4: Process parameter for loading of drug into the Nanosponges

Batches (Ratio)	F1 (1:1)	F2 (1:2)	F3 (1:3)	F4 (1:4)
Drug (mg)	40	40	40	40
Placebo (mg)	40	80	120	160

Febuxostat and placebo nanosponges were measured in various ratios in the range of 1:1 to 1:4, then combined with a methanol-water solution. This was followed by agitation with a motorized stirrer for around four to five hours at ambient temperature to enhance the loading of the drug. After the designated duration, it was filtered via Whatman filter paper, and the resulting remainder was desiccated for subsequent application.

Characterization of FEB-loaded NS

The formulated preparations were assessed based on several physicochemical properties, including yield percentage, drug loading, as well as particle size. A structural examination was conducted utilizing different analytical tests and methods like FTIR, XRD, etc.

Assessment of % Yield, Drug Loading, Particle Size

The initial weight of the solid materials used and the total weight of the dry NS were used to calculate the percent yield of the NS Formulations.

$$\text{Percent Yield} = \frac{\text{Actual Yield}}{\text{Theoretical Yield}} \times 100$$

Percent drug loading was evaluated using the equation.

$$\text{Drug loading} = \frac{\text{Drug Content of NS}}{\text{Weight of NS recovered}} \times 100$$

The particle sizes were measured by diluting water-based dispersions to a certain scattering amplitude at 25°C. Then, dynamic scattering of light measures with a zeta sizer were used to find the nanoparticles' mean diameter.

Morphological Analysis

Morphological investigations of particular NS formulations were performed utilizing Differential scanning calorimetry on the pure drug, pure polymer, a physical mixture of drug and polymer (1:1), and drug nanosponges to assess the alterations occurring during nanosponges formation and the

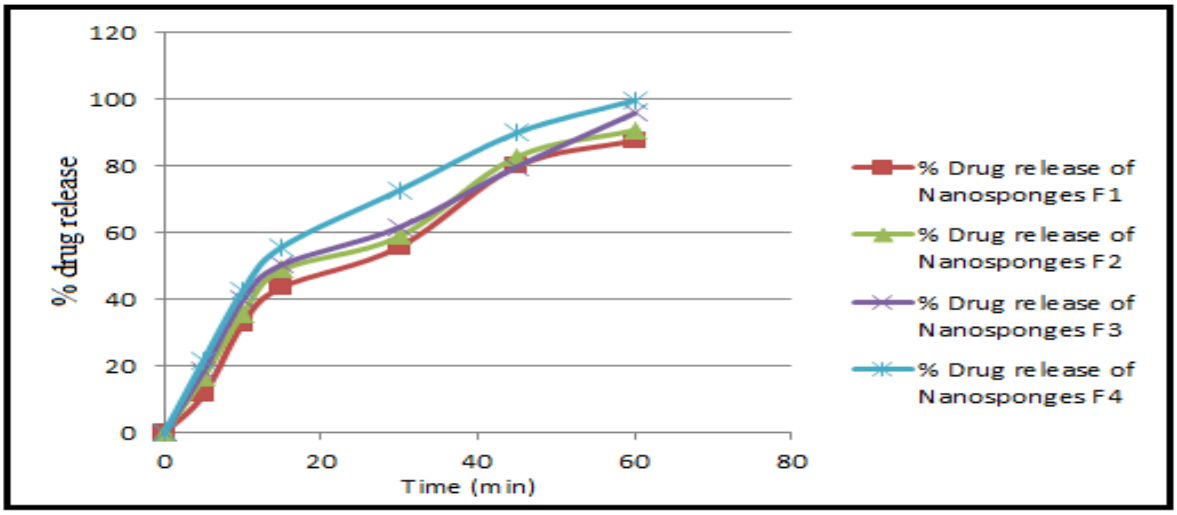

Figure 5: Graphical presentation of comparative drug release profile for Febuxostat nanosponges of F1 to F4 formulations

Table 5: Characterization of Nanoparticles

Sr. No.	Batch	Zeta potential of Febuxostat nanosponges (mV)	Yield (%) of Febuxostat	Drug content (%) of Febuxostat	Particle size (nm) of Febuxostat nanosponges
1.	F1	-18	72.89±0.12	77.78±0.021	130±0.04
2.	F2	-20	80.45±0.014	69.90±0.074	107±0.01
3.	F3	-11	88.89±0.09	81.24±0.011	99±0.03
4.	F4	-15	72.89±0.25	86.79±0.008	94±0.04

Table 6: XRD Data of Febuxostat (Pure Drug) and Febuxostat Nanosponges

Parameter	Febuxostat (Pure Drug)	Febuxostat Nanosponges
Peak Position (2θ °)	~9°, ~11°, ~22°, ~28-30°	~20° to ~35°
Peak Intensity	Strong, sharp peaks	Reduced intensity, broader peaks
Crystallinity	High	Reduced (Partial amorphization)
Sharpness of Peaks	Well-defined	Less defined, diffused
Structural Interpretation	Crystalline nature	Partial loss of crystallinity due to nanosponge entrapment
Effect on Drug Properties	Poor solubility	Improved solubility due to reduced crystallinity

mechanisms underlying the enhanced drug solubility. A DSC reference pan was used for specimen analysis, and DSC curves were procured utilizing a suitable differential scanning calorimeter DSC-61000 (Metller Toledo USA).
The samples were heated using a proper nitrogen flow (10 ml/min) at a scanning speed of 10^0C/ min ranging from 25º C -300º C. The reference utilized was an empty aluminum pan. Powders of the plain drug, polymers, and particular nanostructured preparations were examined utilizing an X-Ray diffractometer. The Fourier transform infrared study of materials was conducted on the Agilent Technologies Cary 630 FTIR spectrophotometer. The spectra of nanosponges were captured and examined within the range of 4000 cm^{-1} to 650 cm^{-1}.

***In-vitro* Drug Dissolution Release Study**

These studies of powdered NS formulation samples were conducted using a USP type II apparatus. Dissolution was conducted at 37 ± 0.5°C with the speed of paddle being 50 rpm, utilizing 900 mL of phosphate buffer having pH 7.2, as the dissolution media. 5 ml samples were extracted at specified time periods and were replaced with an equal volume of new, dissolving media which was preheated at 37 ± 0.2°C to preserve sink conditions. The samples were filtered using a 0.45 µm membrane filter and then evaluated with a calibration curve exhibiting a R^2 value of 0.998 at λmax 317 nm. Every experiment was conducted in duplicate.
Triplicate *in vitro* release tests were carried out in 900 ml of a phosphate buffer solution with a pH of 6.8 employing the USP Paddle technique at fifty revolutions per minute and 37±0.2degrees Celsius. At 5, 10, 15-, 30-, 45-, and 60-minute periods, specimens were collected at the proper times. Spectrophotometric measurements were taken at 312 nm for the samples. To adjust for volume, fresh dissolving media was introduced every time a sample was collected.

Experimental Design and Data Analysis

A factorial design is a technique employed to assess two or more elements concurrently, facilitating the simultaneous evaluation of the effects of many components and their interactions. Factors may be qualitative or quantitative, with their levels representing the values or designations attributed to them. Factorial trials encompass every possible combination of all levels across all factors. The effect of a factor refers to the alteration in reaction resulting from modifications in the level(s) of that factor. The optimization of pharmaceutical formulations is essential for formulation research, with the aim of creating a mathematical model that characterizes the reactions. The optimization study utilized Design Expert® software, employing a 2-factor 3-level complete factorial design for a systematic examination of polymer combinations. Polynomial models for all response variables were developed using multiple linear regression studies, with statistical validity confirmed using ANOVA. The ideal mathematical representation was chosen on many statistical metrics, including the coefficient of variation, multiple correlation coefficient., etc.
This study aimed to achieve an optimized formulation for Febuxostat solid dispersion by determining the effect of some factor (variable) and interaction during the process of

Table 7: *In- vitro* drug release studies of different batches of Febuxostat nanosponges

Time (min)	% Drug release of nanosponges			
	F1	F2	F3	F4
0	0	0	0	0
5	11.45	16.78	18.78	21.78
10	32.78	35.78	39.89	42.56
15	43.65	48.89	50.43	55.78
30	55.76	58.90	61.67	72.78
45	79.98	82.78	79.86	89.98
60	87.76	90.78	95.89	99.78

Table 8: Pre-compression evaluation of powder blend formulation

Sr.No.	Parameter	Febuxostat	Nanosponges
1	Angle of repose	31.54º	26.87º
	Inference	Passable	Good
2	Bulk density (gm/ml)	0.17	0.1
3	Tapped density (gm/ml)	0.27	0.118
4	Carr's index (%)	26	15.79
	Inference	Poor	Good
5	Hausner's ratio	1.34	1.13
	Inference	Poor	Good

Table 9: Post compression evaluation of Febuxostat nanosponges tablet formulations

Formulation batches	Weight variation (mg)	Hardness (kg/cm^2)	Friabili ty (%)	Thickness (mm)	Drug content (%)
F1	0.361±0.02	3.8	0.63	3.11±0.014	98.4
F2	0.363±0.04	3.9	0.65	3.12±0.012	97.2
F3	0.355±0.03	3.9	0.55	3.21±0.016	98.0
F4	0.359±0.06	4.0	0.61	3.12±0.012	96.2
F5	0.361±0.03	4.1	0.62	3.15±0.020	98.2
F6	0.354±0.04	4.2	0.56	3.20±0.024	95.2
F7	0.360±0.07	4.3	0.65	3.25±0.018	98.2
F8	0.361±0.08	4.4	0.55	3.30±0.010	98.4
F9	0.366±0.05	4.4	0.61	3.10±0.012	95.4

Table 10: In vitro dissolution of Febuxostat nanosponges tablet for F1-F9 batch

Time	Percentage drug Release								
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	1.25	2.56	1.86	3.56	4.56	2.87	5.51	6.75	4.99
2	18.86	15.65	17.86	13.56	18.96	19.84	17.89	14.58	17.96
3	28.98	31.97	29.34	37.62	29.66	29.52	25.53	29.55	29.05
4	39.86	36.86	37.89	41.25	37.89	33.65	38.95	36.86	38.88
5	45.80	45.75	48.31	45.40	47.98	41.94	46.85	40.43	49.23
6	58.98	54.65	58.62	57.65	55.63	56.23	53.54	59.86	57.86
7	69.95	66.56	67.23	64.56	68.69	63.65	64.53	62.23	66.86
8	70.23	67.12	70.45	68.65	72.30	67.69	66.25	63.63	67.54
9	75.89	72.69	78.95	75.65	79.62	75.96	77.96	70.95	76.96
10	84.96	81.95	84.68	86.86	88.96	84.63	86.69	80.65	86.98
11	92.56	90.56	94.86	95.65	96.56	92.29	94.65	91.23	94.85
12	99.20	98.39	96.89	98.34	98.26	97.86	98.3	98.01	98.27

Table 11: The kinetic release data

Zero order Equation line Y=	R2	First order Equation line Y=	R2	Higuchi equation line Y=	R2	Korsmeyers peppas Equation line Y=	R2
Y=8.3812x+2.7323	0.9755	Y=0.1135x+0.8759	0.6068	Y=39.066x-38.006	0.9942	Y=1.4841x+0.5404	0.8597

preparation of solid dispersion. Meanwhile the solid dispersion was being processed; the impact of different factor had been evaluated by making change in their quality and in their quantity. Finally, two of the most significant factors had been chosen as the independent variable. In next step, for determining the low and high levels of each factor, some formulations were made, and the results are listed in table 1.

An experimental grid was created utilizing the 3^2 factorial design with two variables, employing the Design Expert 7.0.0 software, resulting in the execution of 9 experiments. For FEB nanosponges, F1 batch was optimised batch on the basis of particle size (lowest), drug release (highest), zeta potential (stable) and drug content (highest). This batch was further used to prepare the naosponge tablet. (F1 to F9).

From the drug content, drug release and hardness: F3 batch of nanosponge tablet was found to be optimized.

Formulation and Preparation of Febuxostat Nanosponges Tablet

The nanosponges' ratio indicated that the formulation yielded the most favorable results in dissolution and solubility experiments. The febuxostat tablets were prepared using the Febuxostat nanosponges. The ingredients for tablet manufacture are illustrated in Table 1. Each tablet component was sieved via a sieve with a mesh size of # 60, then weighed accurately, combined, followed by compaction into tablets employing a 10 mm punch using a rotary tablet minipress.

Manufacturing the Tablet using the Direct Compression Method

Weigh each ingredient precisely. The geometric dilution technique was employed to blend all of the granules using a pestle and mortar. The powder was directly compressed using the direct compression procedure after applying the binder.

RESULTS AND DISCUSSIONS

Production and Physicochemical Assessment of NS Preparation

Solvent diffusion is cost-effective and suitable for drugs with limited solubility, which belongs to BCS class II drugs. The solvent diffusion technique was selected for the preparation of FEB-loaded nanosponges using a 1:2 ratio of β-cyclodextrin and dichloromethane. Different placebos were prepared using different polymers and cross-linkers.

All the placebos were observed under a motic microscope for nature and particle size. From the above observation, it was concluded that cyclodextrin polymer and dichloromethane were best suited for further formulation and evaluation because of their spongy nature and particle

size in nm. Using a stirrer that is mechanical, the drug could be loaded into the nanosponges. Combine the medicine and placebo in a beaker with a methanol-water combination at varying weight ratios, ranging from 1:1 - 1:4. Allow the drug loading process to complete by stirring it mechanically at room temperature for four to five hours. After passing the mixture through whatmann filter paper, the leftover residue was dried.

Formulations (F4 and F3) that have an identical amount of drug with ethyl cellulose (EC) have greater values for entrapment efficiency and the loading of the dtug, which demonstrates that these frameworks are reliant on the drug to polymer ratio. This proves that the medication content per unit of polymer is a critical component in this regard. Contrary to previous research, which found that increasing the drug-to-polymer ratio improved entrapment efficiency and drug loading, our findings show the opposite. Additionally, it was discovered that the percentage yield of the created formulations was influenced by the drug to polymer ratio. This parameter's values for NS formulations were found to be between 72% and 88%. It is possible that the product's adhesive properties account for the low % yield statistics. A decrease in percent yield was caused by foaming and aggregation, which adhered part of the product with the apparatus. Nanoparticle stability is heavily influenced by the Zeta Potential, which is a measurement of the surface charge. All of the developed formulations display stable formulations with Zeta potential values ranging from -11 to -20 mV, according to our results (Table 5).

Structural Analysis

FTIR

The FT-IR spectra of pure Febuxostat was taken and analyzed between 4000 cm^{-1}-650cm $^{-1.}$ Additionally, the spectra of β-cyclodextrin were taken and was found to be between 4000 cm^{-1} -650 cm^{-1}.

Table 12: Model fitting of Optimize Batch of Febuxostat formulation

Run	Zero order	1st order	Higuchi	Korsmeryspeppas
(R^2)	0.9755	0.6068	0.9942	0.8597

Table 13: Stability study of Optimized Batch of Febuxostat formulation

Time (day)	Drug content (%)	In vitro drug release (%)
0	99.29	99.34
30	98.97	98.92
60	97.62	97.05
90	96.89	96.90

Differential Scanning Calorimetry

This test was conducted on β-cyclodextrin and febuxostat. The DSC evaluation was performed using the analyzer DSC-61000 (Mettler Toledo USA).

Thermogram A shows solvent evaporation near 60-100°C, while Thermogram B confirms Febuxostat's melting point at 208°C. Thermogram C shows water loss from Cyclodextrin due to its hygroscopic nature. Thermogram D shows dehydration due to cyclodextrins' hygroscopic nature. The range of 160-220°C shows thermal stability, while beyond 250°C, cyclodextrin breakdown indicates polymer breakdown.

X-Ray Diffraction Studies (XRD)

This was performed to analyze the physical properties of the drug and its nanosponges.

***In-Vitro* Dissolution Release Studies**

These studies are fundamental in pharmaceutical research and development, providing insights into drug dissolution, absorption, and therapeutic effectiveness. They help ensure that formulations meet the required standards for safety, efficacy, as well as stability.

Evaluation of NS Tablets

Pre-Compression Evaluation

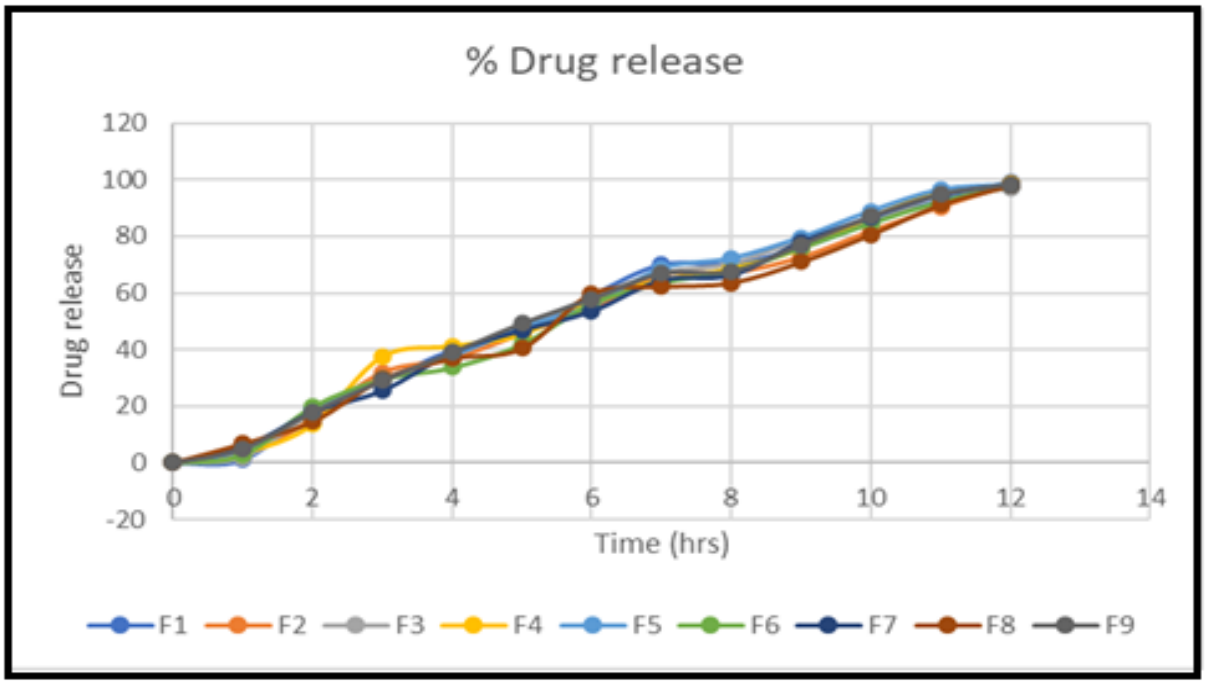

Figure 6: In-*Vitro* Drug Release of different batches

The angle of repose, Carr's index, and Hausner's ratio for all of the formulation mixtures were evaluated. Table 8 displays the findings. Drawing on data from the parametrs it is evident that nanosponges and the mixtures with various formulary elements possess outstanding flow characteristics and fair to good compressible properties. As a result, these blends are suitable for direct compression into tablets, offering smooth hopper flow and uniform content in the final product.

Post Compression Evaluation

After compression, evaluation was performed using a battery of compendia tests, including those for hardness, friability, weight variation, and content uniformity of formed tablets. Table displays the findings. According to USP 30 (2007), all of the variables were inside the specified range.

Dissolution Testing of the NS Tablets

***In-Vitro* Drug Release Study**

The release rate data obtained was subjected to zero order, first order, higuchi and korsmeyer's peppas as illustrated in Table 11.

F1 Batch

Higuchi > Zero order > Korsmeyer-Peppas > first order

From the R^2 value it can be said that the drug release characteristics of the optimized batch of Febuxostat followed Higuchi model kinetics & release pattern respectively.

Stability Studies

In accordance with ICH requirements, stability experiments were conducted on the optimized formulation. We assessed a number of measures prior to and after 30, 60, as well as 90 days of stability, including drug content and in vitro drug release. You can see the results of the stability investigations in the table below. After subjecting the system to conditions of elevated temperature and humidity, stability tests revealed that the aforementioned parameters did not undergo any notable changes. Stability experiments have shown that the produced formulation remains stable even when exposed to high levels of humidity and heat. Conditions: (Heat: 40°C ± 2°C, Humidity: 75% ± 5%). Circumstances of high temperature and moisture had little effect on the stability investigation of the optimized batch of februxostat formulation.

CONCLUSION

By combining Febuxostat with Nanosponges, or nano-sized particles, a sustained-release tablet of the drug was manufactured. The research here employs EC in a polymer capacity. A top method for working with these polymers is the solvent diffusion technique. The produced nanoparticles were round and had a porous structure. The release profile of NS was shown to be more linear compared to the pure drug, according to investigations on intrinsic dissolution. After in-vitro drug release was used to validate the sustained release profile, it was proved to be accurate. As a final dose form, NS tablets were manufactured with all formulation characteristics within the specified limits. The NS-based approach is deemed more suitable for the development and formulation of sustained-release tablets of FEB. Future bioavailability studies with animal models may be conducted to anticipate the pharmacokinetic profile of these specialized systems.

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