FORMULATION AND CHARACTERIZATION OF FEBUXOSTAT AND IBUPROFEN LOADED TOPICAL HYDROGEL FOR TRANSDERMAL POTENTIAL AND ANTIGOUT EFFICACY.

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ABSTRACT:

Gout is a metabolic condition that results in joint inflammation. Taking painkillers or anti-inflammatory drugs can help reduce the pain. It is the kind of arthritis that is most understood and explained. Febuxostat acts on COX enzymes by inhibiting synthesis of uric acid in blood and Ibuprofen minimizes inflammation in joints by avoiding first pass metabolism. A hydrogel formulation was prepared using a combination of drug and polymers, including Febuxostat and Ibuprofen were incorporated into the hydrogel at optimized concentrations which are soluble in hydrophilic polymer PEG 400, hydroxypropyl methylcellulose (HPMC) and Carbopol 934 respectively. The formulated hydrogel was characterized for its physicochemical properties, including viscosity, pH, % drug content, melting point, Zeta Potential, *In -Vitro* Drug Release, *Ex- Vivo* Skin Permeation.

KEYWORDS: Gout, Febuxostat, Ibuprofen, Topical Hydrogel, PEG 400.

INTRODUCTION:

Hydrogels consist of polymer network that absorbs and retain vast quantities of water।Hydrophilic groups in the polymeric network hydrate in aqueous environments to form a hydrogel structure(Ahmed 2015a). Another description is that it is a polymeric material that will no dissolve in water but shows the ability to expand and keep a large amount of water inside its structure. Because of their high-water content, they are quite flexible, much like genuine tissue. The hydrophilic functional group affixed to the polymeric backbone gives its ability to absorb water, whilst the crosslinks interconnected network chains provide it its opposition to dissolution[1]. A type of arthritis called gout is caused by the formation of monosodium urate (MSU) crystals in the joints[2]. When the concentration of uric acid at physiological pH exceeds its solubility limit, which is 6.7-7 mg/dl, it may nucleate and form crystals in tissues।and joints[3].

The human purine metabolism culminates in uric acid, which is produced by the hypoxanthine-xanthine-uric acid cascade. Xanthine oxidase (XO) catalyzes both of the aforementioned reactions. The two pharmacological approaches now used to decrease urate in gout include increasing urine uric acid excretion with a uricosuric drug and decreasing urate synthesis with allopurinol, a xanthine oxidase (XO) inhibitor[4]. Gout treatment usually includes NSAIDS steroids or colchicine, probenecid, allopurinol, and febuxostat।etc[5].

The objective of this study is to formulate and characterize a topical hydrogel containing febuxostat and ibuprofen for transdermal delivery, aiming to enhance antigout efficacy and reduce systemic side effects. The developed hydrogel formulation will be evaluated for its physicochemical properties, in vitro release, and skin permeation characteristics. This study aims to provide a novel and effective topical treatment option for gout patients, minimizing the risks associated with oral administration and improving overall quality of life.

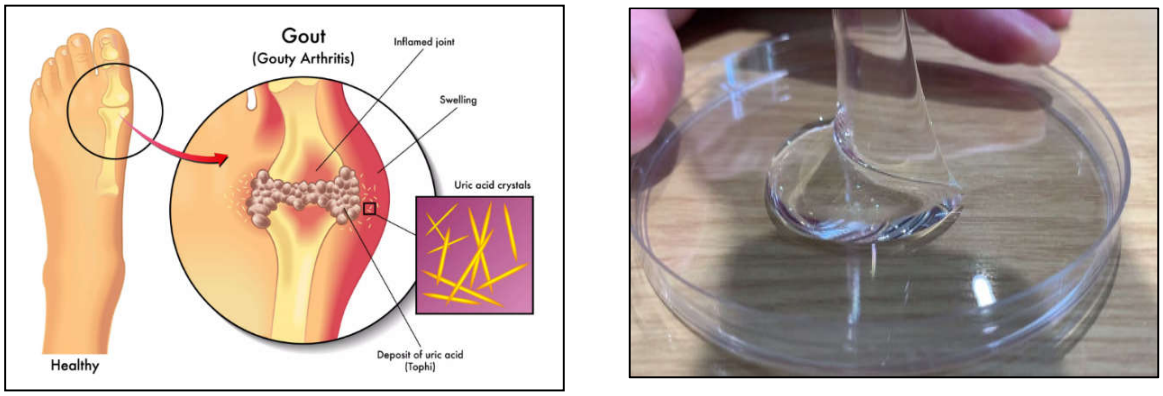

Fig.1: Gout inflammation Characterizes by Topical Hydrogel

MATERIALS &METHODS:

Source of Chemicals:

The materials which are used for preparation of topical hydrogel are as follows:

Table No. 1. List of Material used with their supplier and role.

Sr. No.	Chemicals	Suppliers
1.	Febuxostat	Aarti pharma
2.	Ibuprofen	Sourav chemicals
3.	Polyethylene Glycol 400	Sourav chemicals
4.	Carbopol 934	Sourav chemicals
5.	Hydroxy propyl methyl cellulose	Sourav chemicals

Experimental work:

Physical Characterization of Febuxostat and Ibuprofen:

Physical characterization consists of evaluation of color, odor, appearanceof drug. In this color of drug checked by visual observation and organoleptic characterization of drug.

Determination of Melting Point:

The melting point of Febuxostat and Ibuprofen was determined by Digital Melting Point Apparatus.

Solubility:

As results shown that Febuxostat and Ibuprofen more soluble in hydrophilic polymer polyethylene glycol 400 had the strongest solute-solvent interaction solubility[63]. Based on these findings, PEG-400 appears to be the optimal co-solvent for FBX and IBU, but very soluble in most organic solvents like ethanol, methanol, acetone and dichloromethane.

Analytical Methodology:

UV Spectrophotometric Analysis

Determination of λ max of Febuxostat in Methanol:

Weigh accurately a small amount of febuxostat standard powder and dissolve it in a suitable solvent to prepare a stock solution (e.g.,10 µg/mL).Set up the UV-Vis spectrophotometer to scan a wavelength range (e.g., 200-400 nm) to cover the expected absorbance range of febuxostat.Measure the absorbance of the Febuxostat solution against a blank solvent. Identify the wavelength at which the absorbance is maximum, which is the λmax of Febuxostat.

Calibration curve determination by UV-Vis Spectrophotometry:Febuxostat

Preparation of Stock Solution:

1. Weigh accurately 10 mg of Ibuprofen standard powder.
2. Dissolve the Febuxostat in methanol to prepare a stock solution of 100 µg/ml.

Preparation of standard stock solution: Febuxostat (In Methanol and PBS pH 7.4)

1. Febuxostat 10 mg was accurately weighed and transferred to 100 mL volumetric flask. It was dissolved and diluted up to the mark with solvent to obtain 100 µg/mL as standard stock solution[64].
2. From the stock-I, 10 ml sample was withdrawn by pipette and diluted to 100 ml by using methanol.

Determination of λ max of Ibuprofen in Methanol:

Weigh accurately a small amount of ibuprofen standard powder and dissolve it in a suitable solvent to prepare a stock solution (e.g., 10 µg/mL).Set up the UV-Vis spectrophotometer to scan a wavelength range (e.g., 200-400 nm) to cover the expected absorbance range of ibuprofen.Measure the absorbance of the ibuprofen solution against a blank solvent.Identify the wavelength at which the absorbance is maximum, which is the λmax of Ibuprofen.

Calibration curve determination by UV-Vis Spectrophotometry: Ibuprofen

Preparation of Stock Solution

1. Weigh accurately 10 mg of ibuprofen standard powder.
2. Dissolve the ibuprofen powder in a suitable solvent (e.g., methanol) to prepare a stock solution of 100 µg/ml.

3. Preparation of Standard Solutions

1. Prepare a series of standard solutions by diluting the stock solution to different concentrations (e.g., 10, 20, 30, 40, 50 and 60 µg/ml).
2. Use a suitable solvent to dilute the stock solution.[67]

Differential Scanning Calorimetry:

Differential Scanning Calorimetry (DSC) is a thermal analysis technique used to study the thermal properties of materials. Here's a general outline for conducting DSC analysis on febuxostat and ibuprofen. The interaction studied were carried out using differential scanning calorimetry and DSC curve represented as heat flow v/s temperature.

Drug- Excipient Compatibility Study by FTIR Spectroscopy:

For the purpose of identifying any potential chemical interaction between the drug and the excipients, a method called infrared spectra was used. A physical mixture (1:1) of the drug and its excipients was prepared and mixed. The mixture was scanned using Bruker FTIR Spectrophotometer from 3500-500 cm^{-1}. IR spectrum observed the physical combination was compared to that of the pure drug and excipients.

Formulation of topical hydrogel of Febuxostat and Ibuprofen

Experimental Design[66]

The central composite design was used for optimization of viscosity and drug content for febuxostat and ibuprofen. With the aid of software Design-Expert® (version 13), the trial design was completed. In this design, two factor at 2 different levels were evaluated which gives nine combinations. The amount of Carbopol 934 and HPMC 400, were selected as independent variables.Each factor is studied at low, intermediate and high levels. The dependent variable selected for study viscosity and % Drug Content.

Table No. 2: Independent Variables and their values

Independent Variable	Low level (-)	Intermediate level (±)	High level (+)
X_1=Carbopol 934	0.5%	1.25%	2%
X_2= HPMC	0.5%	1.25%	2%

Table No. 3: Formulation Batches of Hydrogel as per Central Composite Design

SR NO	Formulation Batches	API-Febuxostat	API-Ibuprofen	A: Carbopol 934	B: HPMC
1.	FIH 1	80	80	20	20
2.	FIH 2	80	80	20	5
3.	FIH 3	80	80	5	20
4.	FIH 4	80	80	12.5	12.5
5.	FIH 5	80	80	12.5	20
6.	FIH 6	80	80	5	12.5
7.	FIH 7	80	80	20	12.5
8.	FIH 8	80	80	5	5
9.	FIH 9	80	80	12.5	5

***Note-** Quantity expressed in milligram

Method of Preparation of Hydrogel:

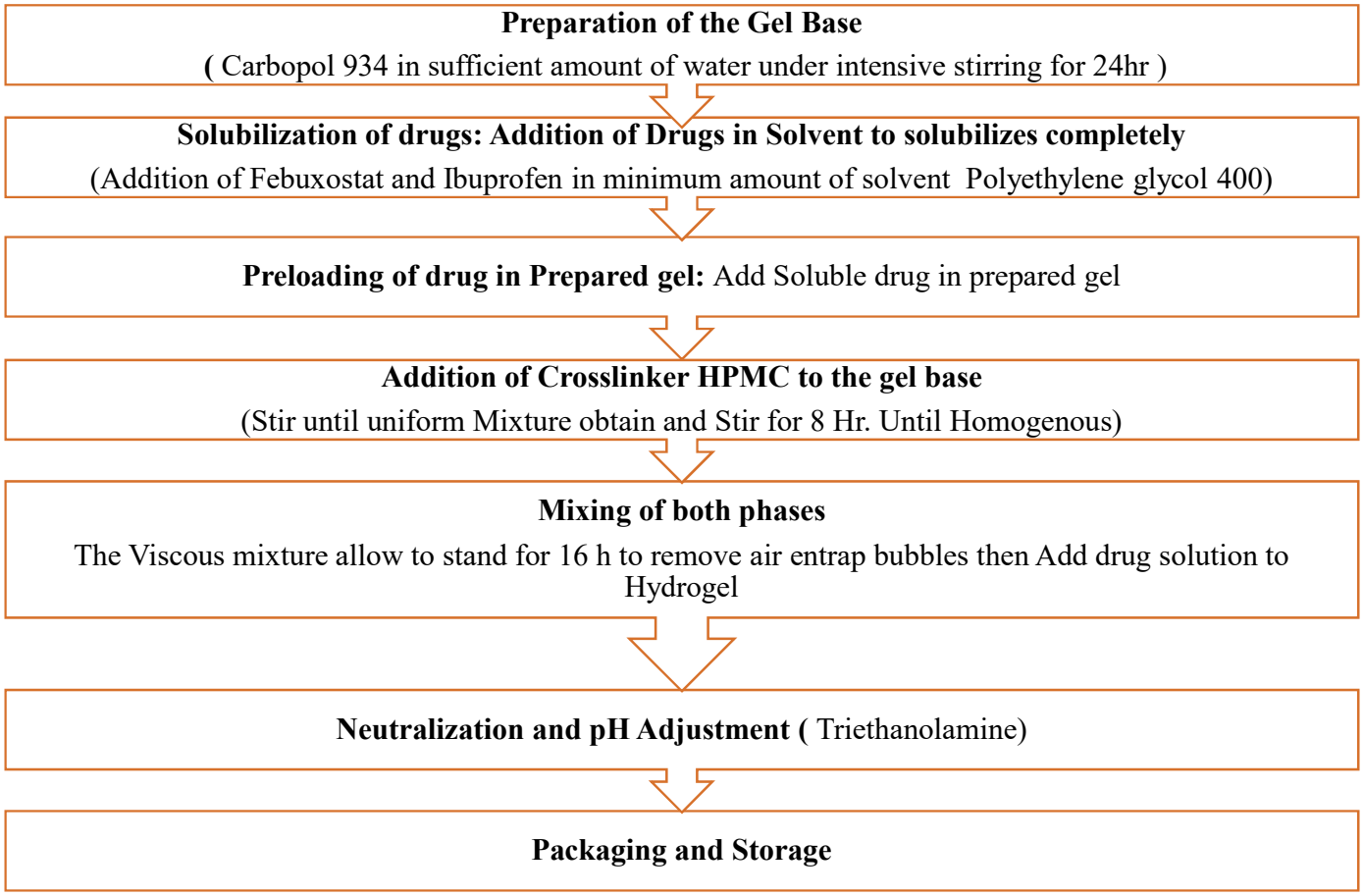

Fig. 2: Method of Preparation of Hydrogel

Solubility:

As results shown that Febuxostat and Ibuprofen more soluble in polyethylene glycol 400 had the strongest solute-solvent interaction solubility[3].Based on these findings, PEG-400 appears to be the optimal co-solvent for FBX and IBU, but very soluble in most organic solvents like ethanol, methanol, acetone and dichloromethane.

Melting Point[4]:

The melting point of febuxostat is typically reported as around 209°C and the Ibuprofen exhibits a melting point range between 75 and 77°C[4].

Calibration curve determination by UV-Vis Spectrophotometry:

Preparation of standard stock solution of febuxostat (in Methanol and PBS pH 7.4) Febuxostat 10 mg was accurately weighed and transferred to 100 mL volumetric flask. It was dissolved and diluted up to the mark with solvent to obtain 100 µg/mL as standard stock solution[5].

FTIR Spectroscopy:

By comparing the spectra, it was possible to determine whether the drug and excipients were compatible. The IR spectra of the pure drug (Febuxostat and Ibuprofen) and excipients, as well as mixtures of the two, were recorded by FTIR.

Differential Scanning Calorimetry:

The structural, crystal and physical state characterization of Febuxostat and Ibuprofen, the DSC study was performed for pure drug, and formulation.

Zeta potential:

Zeta potential is an essential parameter for designing stable, effective, and patient-friendly topical hydrogels. It helps optimize drug delivery, stability, and skin interaction while maintaining the desired physical properties of the formulation.

Viscosity and pH:

Viscosity determines how easily the hydrogel can be spread on the skin. An optimal viscosity ensures the hydrogel stays in place after application without dripping or running.[21] The pH of the hydrogel must match or be close to the skin's natural pH (around 5.5) to avoid irritation or discomfort.The pH was measured in each gel, using a pH meter, which was calibrated before each use with standard buffer solutions at pH 4, 7, 9. The electrode was inserted in to the sample 10 min priors to taking the reading at room temperature.

Spreadability study:

A hydrogel with good spreadability is easier to apply uniformly over the desired area, enhancing user comfort and ensuring consistent application.

***In-Vitro* Drug release study:**

In-vitro drug release will be employing by Franz diffusion cell apparatus. IVDR studies quantify the rate and extent of drug release from the hydrogel matrix, ensuring sustained or controlled delivery based on therapeutic requirements.

Drug Content studies:

These studies ensure that the hydrogel contains the intended amount of drug and releases it effectively, safely, and consistently. Accurate drug content ensures the hydrogel delivers the required therapeutic dose.

Table No. 4: Formulation Table

Run	API Febuxostat	API Ibuprofen	A:Carbopol 934	B:HPMC
	mg	mg	%	%
1	80	80	2	2
2	80	80	2	0.5
3	80	80	0.5	2
4	80	80	1.25	1.25
5	80	80	1.25	2
6	80	80	0.5	1.25
7	80	80	2	1.25
8	80	80	0.5	0.5
9	80	80	1.25	0.5

Result & Discussion:

Pre-formulation Evaluation:

The drug Febuxostat and Ibuprofen was evaluated for physical state, color, odor was noted down.

Table No. 5: Physical Characterization of Drug

Tests	Febuxostat	Ibuprofen
Physical State	White crystalline powder	White crystalline solid
Odour	Odorless	Characteristic
Appearance	Homogeneous texture	Colorless

Determination of Melting Point –

The melting point of Febuxostat & Ibuprofen wasdetermined by using Digital Melting Point Apparatus and was found to be 209.3^{0}C & 76.30^{0}C Respectively.

Table No. 6: Determination of Melting Point.

Sr. No	Standard M.P. (℃)	Observed M.P. (℃)	Mean M.P. (℃)
1	**Febuxostat** 210℃-214 ℃	209.3℃	209.3℃
2		211.4℃	
3		207.2℃	
1	**Ibuprofen** 75℃-78℃	75.9℃	76.30℃
2		76.01℃	
3		77.0℃	

Solubility:

As results shown that Febuxostat and Ibuprofen more soluble in polyethylene glycol 400 had the strongest solute-solvent interaction solubility[11].Based on these findings, PEG-400 appears to be the optimal co-solvent for FBX and IBU, but very soluble in most organic solvents like ethanol, methanol, acetone and dichloromethane.

Table No. 7: Solubility Study

API	Solubility	Solubility In Research
Febuxostat	Freely Soluble in organic Solvents likeN,N-dimethylformamide Methanol, Ethanol etc.	Freely Soluble in lipophilic Solvent like PEG 400 Which Shows Highest Solubility Compare to other solvents
Ibuprofen	Freely Soluble in organic Solvents like methanol, Ethanol, Acetone and Dichloromethane etc.	Freely Soluble in lipophilic Solvent like PEG 400 Which Shows Highest Solubility Compare to other solvents

Calibration curve determination by UV-Vis Spectrophotometry of Febuxostat in methanol:

The table shows the absorbance value of different concentration of febuxostat in methanol at wavelength 312 nm& Ibuprofen in methanol at wavelength 258 nm.

Table No. 8: Calibration curve determination by UV-Vis Spectrophotometry of Febuxostat in methanol

SR. NO	Concentration (µg/ml)	Absorbance 315 nm
1.	2	0.0001
2.	4	0.0017
3.	6	0.0038
4.	8	0.0061
5.	10	0.0085

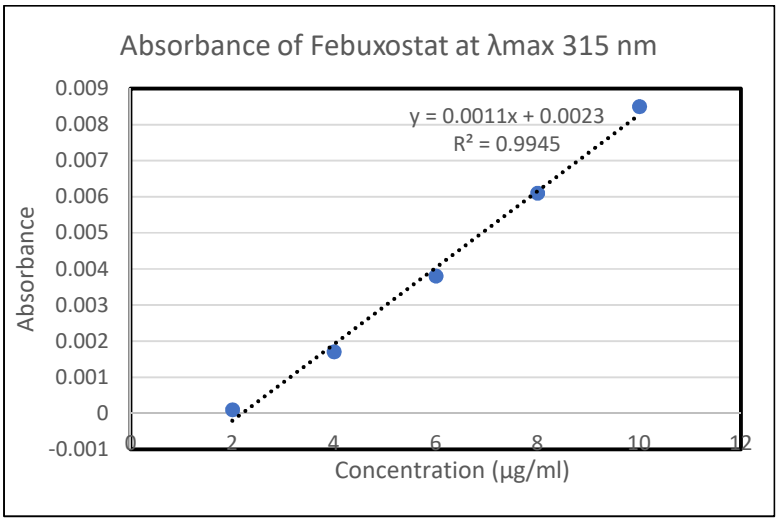

Fig. 3: Calibration curve of Febuxostat in Methanol.

Table No. 9: Calibration curve determination by UV-Vis Spectrophotometry of Ibuprofen in methanol

SR. NO	Concentration (µg/ml)	Absorbance 258 nm
1.	2	0.0101
2.	4	0.015
3.	6	0.021
4.	8	0.0255
5.	10	0.0317

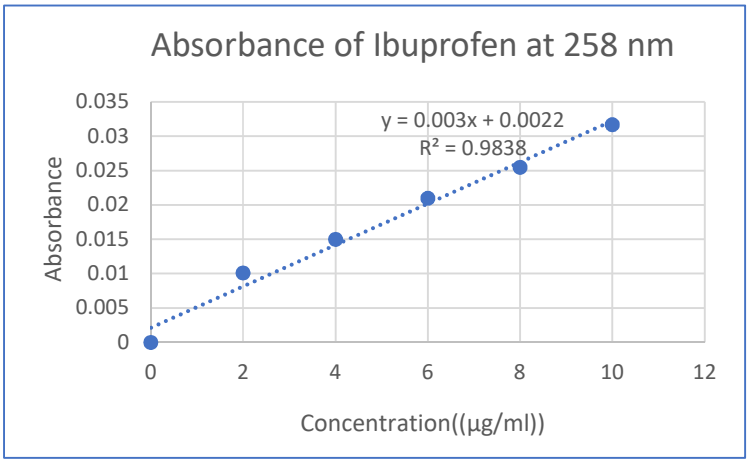

Fig. 4: Calibration curve of ibuprofen in Methanol.

Differential Scanning Calorimetry Study:

Interpretation of Differential Scanning Calorimeter of Febuxostat:

The DSC studies was carried out for pure drug Febuxostat & Ibuprofen. The thermogram revealed that occurrence of sharp endothermic peak at210.93°C.

Table No. 10: DSC Thermogram Peaks

Drug	Melting Point/ temperature (°C)		
Febuxostat	Peak Onset	Peak	Peak Endset
	210.93	211.67	214.57

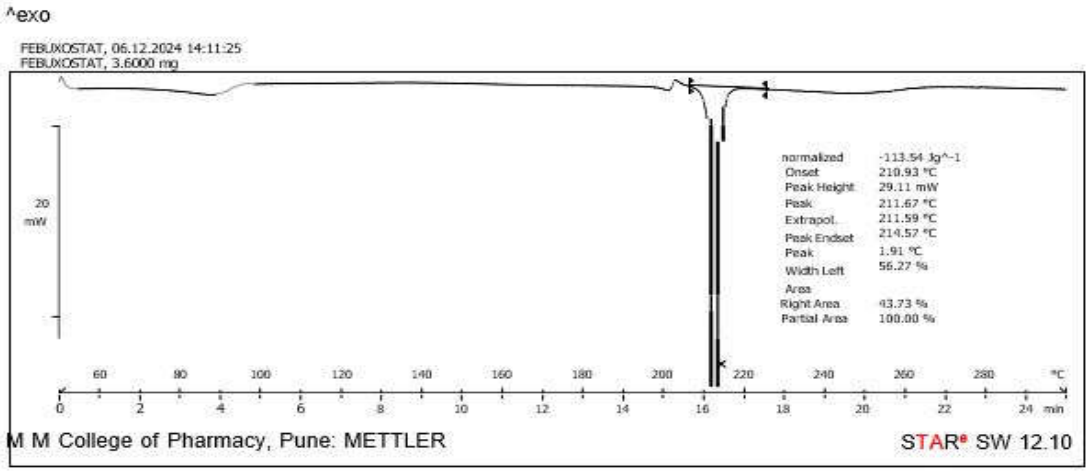

Fig. 5: DSC of Febuxostat.

Fourier Transform Infrared Spectroscopy:

Table No. 11: Compatibility study of Febuxostat by FTIR:

Functional Group	Standard Range (cm^{-1})	Observed Range (cm^{-1})
R-CH_3	3000-2850	2873
C≡N	2300-2200	2234
C=C	1700-1600	1697, 1602
R- O -R	1300-1175	1216
R- S -R	680-610	612
C= N	1790-1690	1697
COOH	1760-1690	1697

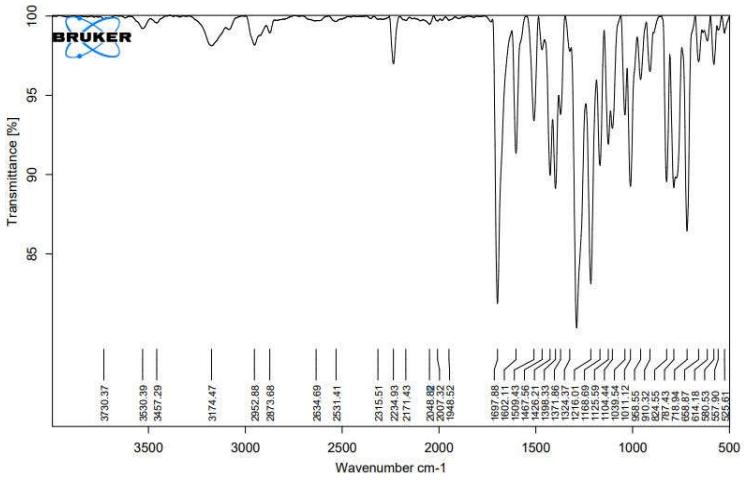

Fig. 6: Interpretation of FT-IR Spectra of Febuxostat.

Table No. 12: Compatibility study of Ibuprofen by FTIR:

Functional Group	Standard Range (cm^{-1})	Observed Range (cm^{-1})
R-CH_3	3000-2850	2869
C=C	1600-1500	1505
C-C	1445-1405	1417
COOH	1760-1690	1706
C-H	2970- 2850	2950

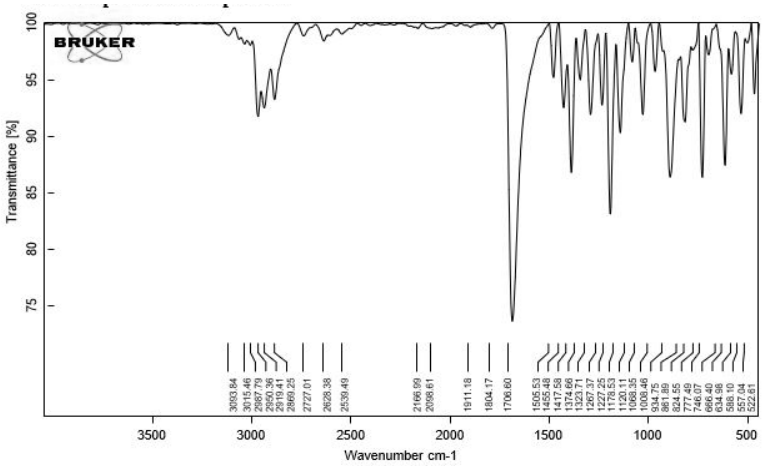

Fig. 7: Interpretation of FT-IR Spectra of Ibuprofen

Characterization of Topical Hydrogel:

Physical Characterization of Topical Hydrogel:

Table No. 13: Physical Characterization of Topical Hydrogel

Sr. No.	Tests	Results
1.	Colour	Translucent White
2.	Odour	odorless
3.	Appearance	Smoothy appears

Table No. 14: Evaluation of hydrogel Formulation.

SR NO	Formulation Batches	pH	Spreadability (gcm/sec)	Viscosity(cPs)	Drug Content (%)
1.	FIH 1	6.8	12.30	7398	75.43
2.	FIH 2	6.7	14.53	11598	91.17
3.	FIH 3	6.6	12.47	5599	82.23
4.	FIH 4	6.52	13.87	7798	86.71
5.	FIH 5	6.04	14.56	4039	87.53
6.	FIH 6	6.89	13.54	4599	83.9
7.	FIH 7	6.42	12.51	7598	88.39
8.	FIH 8	6.91	14.96	3399	89.20
9.	FIH 9	6.73	13.67	4599	82.57

(Note: FIH Stands for Febuxostat Ibuprofen Hydrogel)

Zeta Potential:

The zeta potential of FIH 2 batch was found to be – 10.54 mV. The zeta potential analysis showed that charge present on Hydrogel formulation was stable.

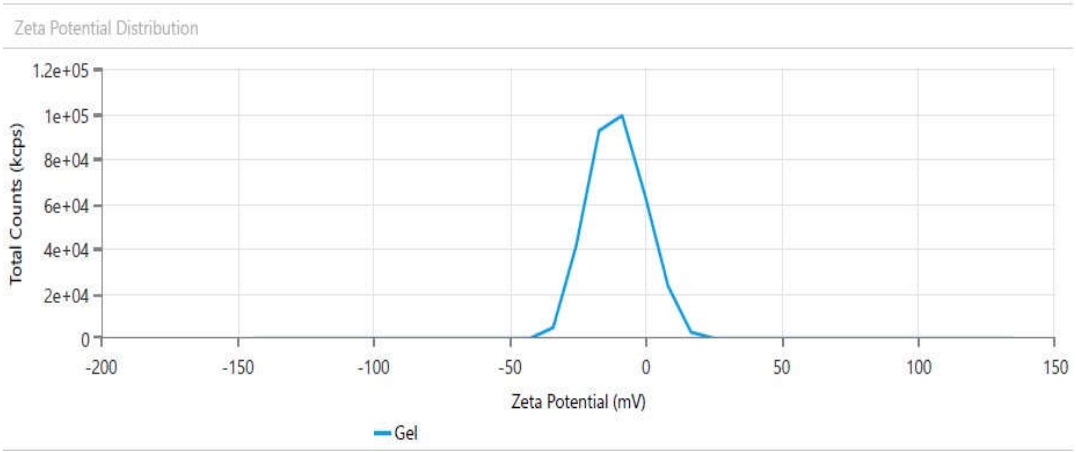

Fig. 8: Zeta Potential Peak

Fig.: Standard result of Zeta Potential.

Name	Mean	Std. Deviation	RSD	Minimum	Maximum
Zeta Potential (mV)	-10.54	-	-	-10.54	-10.54
Zeta peak 1 Mean (mV)	-10.54	-	-	-10.54	-10.54
Conductivity (mS/cm)	0.05562	-	-	0.05562	0.05562
Wall Zeta Potential (mV)	0	-	-	0	0
Zeta Deviation (mV)	10.06	-	-	10.06	10.06
Derived Mean Count Rate (kcps)	2.678E+05	-	-	2.678E+05	2.678E+05
Reference Beam Count Rate (kcps)	1777	-	-	1777	1777
Quality Factor	1.771	-	-	1.771	1.771

***In- Vitro* Drug Release from Topical Hydrogel:**

The *In-vitro* drug release of Topical Hydrogel was found in range of 70.40% to 82.74138% in phosphate buffer pH 6.4 for 6 hours which is shown in following table 7.17. The *in-vitro* drug release of FIH 2 batch of Hydrogel was found high % drug release.

Table No. 16: *In –Vitro* Drug Release of Topical Hydrogel

Sr. No	Time (Min)	FIH 2 (%)	FIH 5 (%)	FIH 8 (%)
1.	30	8.65517	5.05172	6.17241
2.	60	15.2069	11.12069	13.17241
3.	120	23.22414	19.5862	24.91379
4.	180	37.15518	29.74138	36.51724
5.	240	48.4138	41.77586	49.5862
6.	300	66.82759	55.32758	63.06896
7.	360	82.74138	70.4079	78.4427

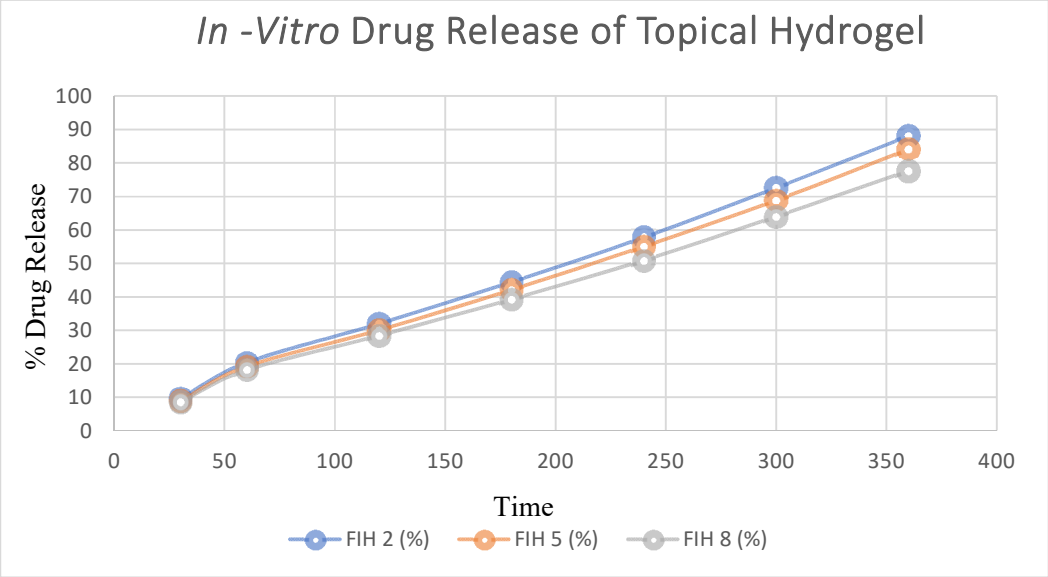

Fig. 9: *In –Vitro* Drug Release of Topical Hydrogel.

***Ex-Vivo* Permeation Study-:**

The *Ex-vivo* permeation studies of FIH 2, FIH 5 and FIH 8 was found in range between 77.651% to 88.03%. From ex-vivo permeability study showed that FIH 2 batch showed high permeability of Hydrogel as compare to Batch FIH 5 and FIH 8.

Table No. 17: *Ex-Vivo* Permeation Study of Topical Hydrogel.

Sr. No	Time (Minn)	FIH 2 (%)	FIH 5 (%)	FIH 8 (%)
1.	30	9.65517	8.96552	8.58662
2.	60	20.3621	19.1897	18.1211
3.	120	31.9828	30.069	28.4314
4.	180	44.4138	42.1035	39.2763
5.	240	57.7759	55.069	50.9314
6.	300	72.58622	68.8448	63.9832
7.	360	88.0345	84.1035	77.6556

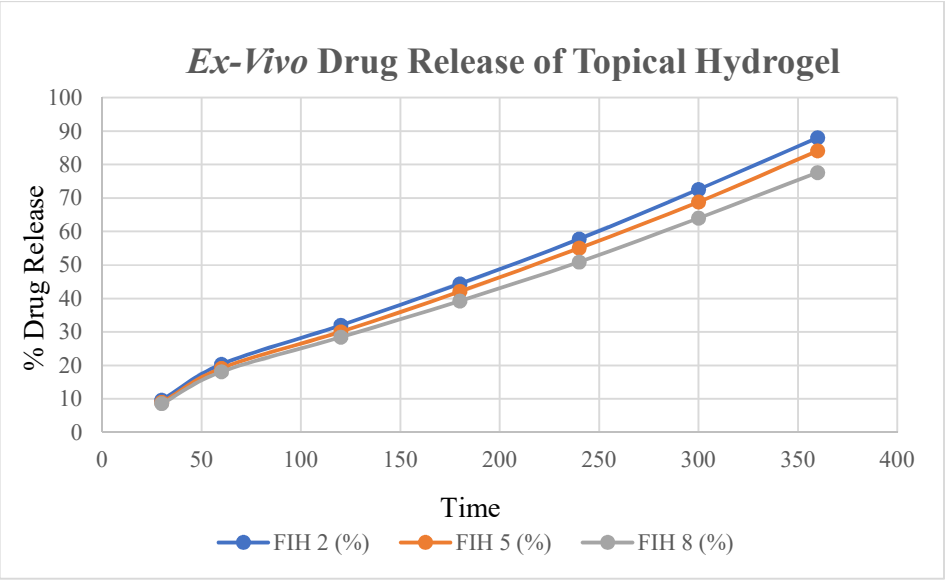

Fig. 10: *Ex-Vivo* Permeation Study of Topical Hydrogel

Table No. 18: Compatibility study of Hydrogel formulation by FTIR:

Table: Interpretation of FTIR spectra of Hydrogel Formulation.

Functional Group	Standard Range (cm^{-1})	Observed Range (cm^{-1})
R-CH_3	3000-2850	2871
C=C	1680-1600	1602
C-C	1445-1405	1423
COOH	1750-1650	1697
O-H	3500-3200	3470
R-O-R	1300-1175	1288
C≡N	2300-2200	2234
C= N	1790-1690	1697
R- S -R	680-610	662
C-H	2970- 2850	2951

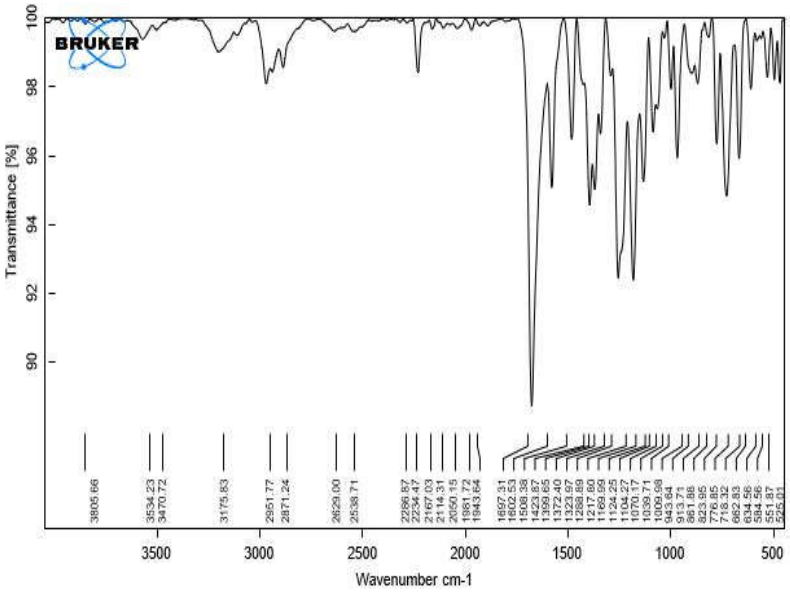

Fig. 11: Interpretation of FTIR spectra of Hydrogel Formulation.

CONCLUSION:

The formulation and characterization of Febuxostat and Ibuprofen loaded topical hydrogel have demonstrated promising results for transdermal potential and anti-gout efficacy. The developed hydrogel formulation has shown satisfactory physicochemical properties, drug contentand in vitro release profile, indicating its potential as a novel therapeutic approach for the treatment of gout and associated inflammatory conditions. The combination of Febuxostat and Ibuprofen in a Topical Hydrogel formulation may provide enhanced therapeutic benefits, improved patient compliance, and reduced side effects, making it a valuable treatment option for patients suffering from gout.

The FIH 2, FIH 5 & FIH 8 Batches of Febuxostat & Ibuprofen Topical hydrogel were optimized based on evaluation criteria. The optimized batch was characterized for its pH, Viscosity, % Drug release, Spreadability, Zeta Potential, *In-Vitro* Drug Release and *Ex- Vivo* Skin Permeation.

The FIH 2 batch of Topical Hydrogel met all physiochemical tests and assessment parameters. It exhibited higher drug release and permeability compared to FIH 5 & FIH 8 batches. Among all batches FIH 2 contains 20mg Carbopol 934 used as gelling agent and 5mg HPMC used as crosslinker which gives better consistency, viscosity and appearance as compare to other batches. Hence, FIH 2 batch gives significant results and optimized as shown by viscosity and % Drug content.

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