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Research Article

**DEVELOPMENT AND CHARACTERIZATION OF  
TRANSDERMAL PATCHES OF FEBUXOSTAT FOR  
TRANSDERMAL DELIVERY**

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(MP) India, 462021, Email-deeptiyadavmdp@gmail.com**Article Received:** September 2021    **Accepted:** September 2021    **Published:** October 2021**Abstract:**

*The aim of this work is to formulate and evaluate transdermal patches containing Febuxostat as active pharmaceutical ingredient. The objective of the present investigation was to evaluate the transdermal films of Febuxostat to its applicability to reduce the dose of the drug. Febuxostat is an orally available non-purine xanthine oxidase (XO) inhibitor that has been indicated in treatment of patients diagnosed with gouty arthritis suffering from hyperuricemia and is used in the chronic management of the disease. The capability to be able to deliver hydrophilic drugs through a transdermal route may furnish a better solution to the problems associated with other methods for delivery of hydrophilic drugs. Due to their low absorption by the GI tract, hydrophilic drugs need to be administered orally in very large doses. This increases the cost of the drug and may carry harmful side effects. Increased efficacy of hydrophilic drugs in TDDS appeals to drug makers, physicians, and patients alike. The development of an effective TDDS, particularly for hydrophilic drugs, will increase the availability of drugs to patients and bring new hydrophilic drugs to the markets which were previous not viable due to their poor bioavailability with oral dosing. The patches were prepared with the help of a various polymers (Ethyl cellulose, Sodium alginate, and Polyethylene glycol 400). The patches FTDP3 were more transparent as compared to the patches. The evaluation parameters of transdermal patches were evaluated like (Weight variation, Thickness, Folding endurance, Moisture content, Drug content and In-Vitro Permeation study etc).*

**Keywords:** Febuxostat, Transdermal Drug Delivery System, Carbopol 934, Transdermal Patches, Gout.**Corresponding author:****Deepti Yadav,**Technocrats Institute of Technology,  
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**INTRODUCTION:**

Transdermal drug delivery systems (TDDS), which may also be called as transdermal patches hereafter, are delivery systems that have been developed to deliver therapeutically sufficient amount of drug through patient's skin.[1] Transdermal delivery bestows advantage over oral and parenteral routes as it enhances patient compliance along with avoiding the first pass metabolism.[2] The first transdermal system approved for use in the United States in 1979 for systemic delivery was a three-day patch to release scopolamine for treating motion sickness. Over two decades from 1979 and 2002, transdermal delivery was a thrust area of research and on average every 2.2 years, a new patch was approved. From 2003 to 2007, the instance of approval almost tripled and a new transdermal delivery system was approved every 7.5 months. It is forecasted that around one billion transdermal patches are manufactured each year in the recent years. The annual market for transdermal patches in US is more than \$3 billion.[3]

**Advantages of TDDS [4-5]:**

Transdermal delivery has not only led to new methodologies for existing therapies but also has presented possibilities other than the traditional oral route which cause metabolism of can in the liver prematurely thereby leading to adversities and side effects. While hypodermic injections are agonizingly painful, may form dangerous medical waste, and present a risk of transmission through the reuse of needles, particularly in developing countries, transdermal delivery is painless, noninvasive, and self-administered. The use of transdermal patch can lengthen the duration of drug release and therapeutic action, reduce administration frequency, and improve patient compliance, all at a fairly inexpensive production cost. Due to the hydrophobicity of the skin, the transdermal systems for delivering large hydrophilic drugs are one of the biggest challenges.

Nevertheless, the capability to be able to deliver hydrophilic drugs through a transdermal route may furnish a better solution to the problems associated with other methods for delivery of hydrophilic drugs.

**Disadvantages of TDDS:**

The drug should possess some desirable physicochemical properties that may enable its infiltration through the stratum corneum. Transdermal delivery is very difficult if more than 10 mg/day dose of the drug is required to produce therapeutic action. Only relatively potent drugs are suitable candidates for TDDS because of the natural limits of drug entry that is presented by the skin's impermeability. Contact

dermatitis may develop in some patients at the site of application due to one or more components of the system, forcing discontinuation.

Before developing a transdermal product, the clinical need for the same has to be examined carefully. The barrier layer functioning of the skin is different for every individual; it may also vary from one application site to another on the same person; and also differs with age.

**Units of Transdermal delivery system [4-6]:**

The primary components that are required to develop a transdermal delivery system include the following:

- Polymeric matrix
- Therapeutically active agent
- Enhancers of skin permeation
- Pressure sensitive adhesive (PSA)
- Backing membranes
- Release liners
- Plasticizers, solvents etc

**Types of Transdermal Delivery Patches [7]:**

Transdermal patches are categorized in to the following classes depending on the reservoir of the drug: 1) Single-layer drug-in-adhesive patches; 2) multi-layer drug-in-adhesive patches; 3) Drug-reservoir in adhesive patches; 4) Drug-matrix in adhesive patches; 5) Vapour patches; 6) Micro reservoir Systems.

**Factors Affecting Transdermal Drug Delivery:**

Apart from minor factors such as individual variations, age, site of application, occlusion, temperature, race, and disease states, there are other physical related factors that affect the permeation of drugs through the skin as described in the Fick's equation:

$$dQ/dt = \frac{P \cdot C \cdot D \cdot A}{l}$$

Where,  $dQ/dt$  is the rate of drug penetration,  $P$  is the partition coefficient between vehicle and stratum corneum,  $C$  is the drug concentration in the vehicle,  $D$  is the average diffusion coefficient,  $A$  is the surface area of application of the drug,  $l$  is the thickness of the skin barrier.

(a) **Partition Coefficient:** It is measured as the octanol-water ratio (or  $\log P$ ) of the drug. It is an indicator of lipophilicity against hydrophilicity.

(b) **Diffusion:**

It is the process by which a substance moves from one area to another. It can be manipulated by thermal stirring and needs a concentration gradient. Alternatively speaking, the area towards which the substance is passing must have a lower concentration of the drug than the area from where it is coming. Lipophilic substances diffuse comfortably across the stratum corneum layer, but have difficulty with the aqueous layers below. If transport slows too much in any of the layers of tissue the process of diffusion slows down, causing a buildup of the drug in the outer layers.

#### (c) Concentration:

It is the amount of drug substance per unit volume of vehicle. The low solubility of drug can become problematic if the vehicle evaporates before the complete partitioning of the drug into the skin, thereby causing precipitation. Therefore, it is necessary to incorporate a small amount of a lesser volatile solvent like fatty acid, terpenes, isopropyl myristate in the transdermal formulation.

#### (d) Surface Area:

Large surface area of contact between the drug formulation and the stratum corneum exposes more drug molecules to the lipid skin layer and so increases the rate of drug permeation.

### MATERIALS AND METHODS:

**Chemicals:** Febuxostat was obtained as a generous gift sample from Ranbaxy, Mumbai, Ethyl cellulose and sodium alginate were purchased from Central drug house Pvt. Ltd., New Delhi. Polyethylene Glycol (PEG 400) was purchased from Merck India Ltd. Acetone, methanol, ethanol, hydrochloric acid, sodium hydroxide, potassium dihydrogen phosphate, sodium chloride and all the other chemicals required were purchased from Oxford Lab Fine Chemicals LLP, Maharashtra. Distilled water prepared using glass distillation unit was used throughout the study.

#### Instruments and Equipments:

- Magnetic Stirrer 2MLH, REMI Motors Ltd., Mumbai.
- UV-1700 SHIMADZU, UV Spectrophotometer, Japan.
- pH Meter, Labtronics, NewDelhi
- Vortex Shaker, Sentwin India, Haryana.
- Franz diffusion cell (Fabricated).

#### Preparation of reagents [8]:

##### pH 6.8 Phosphate buffer:

44.8 mL of 0.1M NaOH (0.4 g in 100 mL of distilled water) were dissolved in 100 mL of 0.1 M  $\text{KH}_2\text{PO}_4$

(1.361 g in 100 mL of distilled water) and volume was made up to 200 ml with distilled water.

##### pH 7.2 Phosphate buffer:

69.4 mL of 0.1M NaOH (0.4 g in 100 mL of distilled water) was dissolved in 100 mL of 0.1 M  $\text{KH}_2\text{PO}_4$  (1.361 g in 100 mL of distilled water) and final volume was made up to 200 mL with distilled water.

##### pH 7.4 Phosphate buffer Saline:

2.38 g  $\text{Na}_2\text{HPO}_4$ , 8 g NaCl and 0.19 g  $\text{KH}_2\text{PO}_4$  were dissolved in 1000 ml of distilled water to prepare the buffer solution of desired pH.

#### Preformulation Studies [9]:

The preformulation study was carried out with respect to tests of identification such as appearance, melting point and FTIR spectroscopy. It also includes solubility profile of drug in various solvent systems, determination of partition coefficient and quantitative estimation of drug.

#### Physical Characterization:

- Color & State- A small portion of Febuxostat was placed on butter paper and observed in well-lit area.
- Taste & Odor- A very small portion of Febuxostat was tasted with the help of tongue and it was also inhaled to observe the odor.

#### Solubility Profile of Drug:

A qualitative assessment of the solubility of Febuxostat was studied by addition of solvent in small increments to the test-tube containing a fixed amount of drug or vice-versa. After each addendum, the mixture was shaken vigorously and visually inspected for any the presence of any undissolved solute particles.

#### Melting Point:

The melting point of the Febuxostat sample was assessed by open capillary method and the result was reported uncorrected.

#### Partition Coefficient:

The partition coefficient of Febuxostat was performed by using octanol (10 ml) and water (10 ml) as the oil and aqueous phase respectively. Both the phases were mixed by shaking vigorously using a separating funnel and then 5 mg of the drug was mixed to it. The drug was allowed to dissolve in both the phases by shaking and allowing equilibration. Both phases were taken in a conical flask and then analyzed against their respective blank solution and the partition coefficient was calculated by the use of the formula as under

$K_{o/w}$  = Concentration of drug in octanol/  
Concentration of drug in water

#### Calibration curve of Febuxostat in Various Solvents Systems:

- **Standard curve in ethanol:**

5 mg of the drug was dissolved in 10 ml ethanol and dilution was made by taking 1 ml stock and diluting it up to 10 ml with ethanol. Then 0.5, 1.0, 2.0, 5.0, 10  $\mu\text{g/ml}$  solution were made and the absorbance of each was of these aliquots measured by UV visible spectrophotometer at 315 nm and standard plots was made (abs. v/s conc.).

- **Calibration curve in buffer (pH 6.8, 7.2 & 7.4)**

5 mg of the drug was dissolved in 10 mL DMSO and the volume was made up to 100 mL with the solution of buffer (pH 6.8, 7.2 & 7.4). These stock solutions were used to prepare working standards of 0.4, 0.6, 1.0, 2.0, 3.0  $\mu\text{g/ml}$  concentration. The absorbance for these aliquots was measured using UV-visible spectrophotometer at 315 nm and the calibration curves were plotted.

#### FTIR spectral analysis:

The FTIR spectrum of Febuxostat was obtained using Bruker alpha spectrophotometer and the presence of various functional groups was ascertained.

#### Formulation of Transdermal Patch [10]:

Transdermal patches loaded with Febuxostat were prepared by the use of solvent casting method in Petri plates. The backing layer was casted by pouring 4% PVA solution on the Petri plates lined with aluminum foil followed by drying at 60°C for 3-4 hrs in hot air oven. All the ingredients were weighed accurately and blended by triturating in pestle and mortar. The mixture was gradually added to a magnetically stirred solvent system containing the plasticizer. The stirring was continued until a clear solution was obtained. This solution was then quantitatively transferred to the prepared Petri plates. The Petri plates were covered with inverted funnels in order to permit controlled evaporation of solvents. The Petri plates were left undisturbed at room temperature for 1- 2 days for complete drying of the patch. The composition of various formulations is presented in Table 1.

**Table 1: Composition of Transdermal patch formulations**

S.No	Formulation	Ratio of Polymer (SA: EC)	Total wt. of Polymers (mg)	Solvent (Ethanol) (ml)	Plasticizer (PEG-400) (mg)	Drug (mg)
1	FTDP 1	4:6	630	30	230	40
2	FTDP 2	5:5	630	30	230	40
3	FTDP 3	6:4	630	30	230	40
4	FTDP 4	7:3	630	30	230	40
5	FTDP 5	8:2	630	30	230	40

#### Evaluation of Transdermal Patches [11]:

##### Uniformity of weight test:

The prepared patches were exposed to testing of mass variation by weighing individually the randomly selected patches (41.8  $\text{cm}^2$ ). These determinations were carried out for each formulation.

##### Thickness:

The thickness of each patch was determined by the use of a Vernier calliper at various positions of the patch and the average thickness was then calculated.

##### Folding endurance:

Folding endurance was assessed by again and again folding a patch from the same place till it breaks. The number of folds that could be made at the same place

without breaking/ cracking gives the value of folding endurance.

##### Drug content test

Three pieces of 0.64  $\text{cm}^2$  were collected by cutting off from different parts of patch from each patch. These pieces were dissolved in 10 ml DMSO and were placed on vortex shaker for 1 h to dissolve completely the patches. The resultant solutions were filtered using Whatman filter paper and then 0.1 mL solution was pipette out into another volumetric flask (10 ml) and dilution was embarked up to 10 ml. The solution was suitably diluted and analyzed for Febuxostat using UV spectrophotometer at 315 nm.[12]

##### Moisture Uptake

The prepared patches were accurately weighed and kept in desiccators at a 75% relative humidity conditions maintained by placing a saturated solution of sodium chloride. After 24 h, the patches were reweighed and the moisture uptake percentage was calculated using the following formula.

$$\% \text{ Moisture uptake} = (\text{Final weight} - \text{Initial weight}) / \text{Initial weight} \times 100$$

#### Percentage moisture loss

Three patches were taken from each formulation and accurately weighed and placed in a desiccator along with fused anhydrous calcium chloride. The patches were removed after 72 h and reweighed. The moisture loss percentage was calculated by using the following formula.

$$\% \text{ Moisture loss} = (\text{Initial weight} - \text{Final weight}) / \text{Initial weight} \times 100$$

#### In-Vitro Release Study

In-vitro permeation study of Febuxostat transdermal patches were performed by using Static Franz diffusion cell having a receptor compartment capacity of 60 mL. The formulated patch of surface area 0.64 cm<sup>2</sup> was kept in between the donor compartment and receptor compartments of diffusion cell over a cellulose acetate membrane of pore size 0.45μ and

covered with an aluminum foil. The receptor compartment of diffusion cell was filled with pH 7.4 saline phosphate buffer. The entire assembly was mounted on a magnetic stirrer and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm; the temperature of the solution was maintained at 37 ± 0.5°C. 1 mL aliquots were withdrawn at various predetermined time intervals (0, 1, 2, 3, 4, 5, 10, 24 h) and the drug content was analyzed by UV spectrophotometer at 315 nm. The receptor phase was refreshed with an equal volume of phosphate buffer (37°C) after each sample withdrawal, and the cumulative amount of drug that permeated per square centimeter of patches were plotted against time. Percent drug permeated and log % DRP was calculated and tabulated.

## RESULTS AND DISCUSSION:

### Preformulation Studies:

Preformulation study was performed for Febuxostat for its physical and chemical properties.

### Physical Characterization:

The result obtained from the physical characterization of the pure drug is reported in Table 2

**Table 2: Physical characteristics of Febuxostat**

S.No.	Test	Observation
1.	Color	White
2.	Taste	Bitter
3.	Odor	Odorless
4.	State	Crystalline

### Solubility characteristic of drug:

The solubility of the pure drug was determined in various solvents and the result is reported in table 3.

**Table 3: Solubility of Febuxostat**

S.No.	Solvent	Solubility
1.	Ethanol	Slightly Soluble
2.	DMF	Soluble
3.	DMSO	Soluble
4.	Water	Practically insoluble

### Melting Point:

The temperature at which melting of drug occurred was determined using open capillary method and the result is reported in Table 4.

**Table 4: Melting Point of Febuxostat**

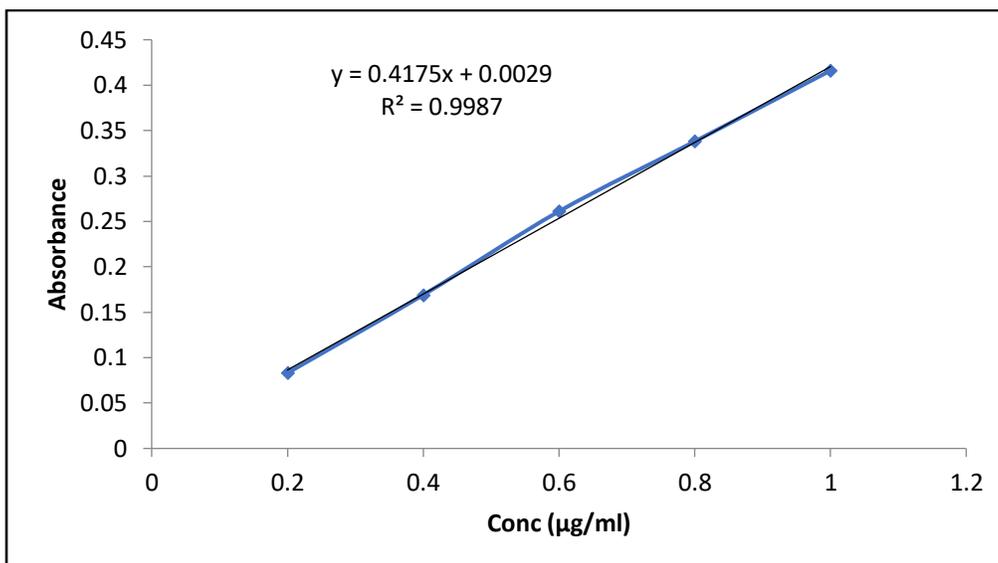
Test	Specification	Observation
Febuxostat	238-239°C	241-243°C

**Partition Coefficient:**

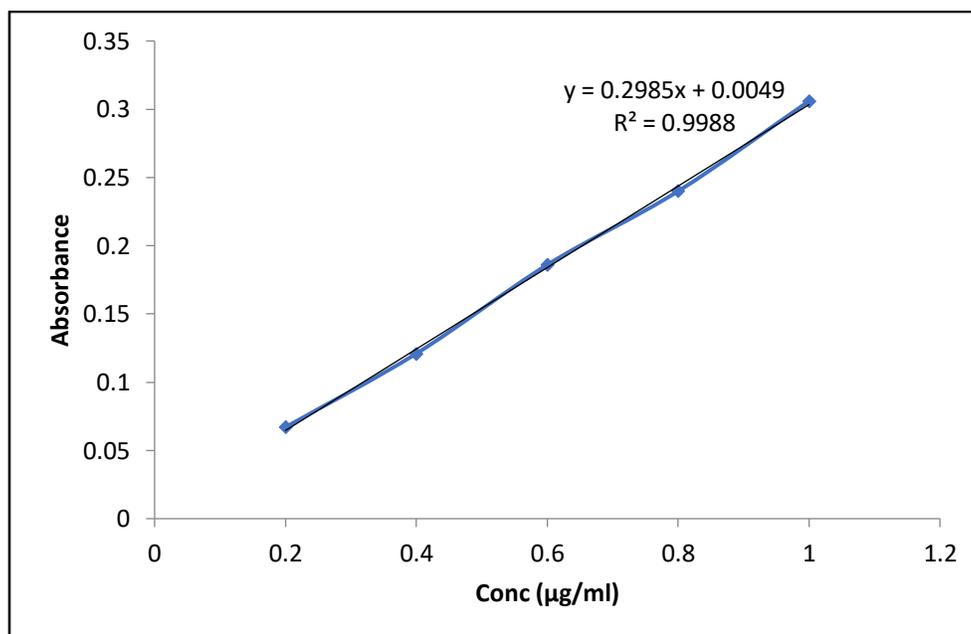
The study for partition coefficient was performed and the log P value was obtained to be **3.2**.

**Calibration Curves of Febuxostat:**

The coefficient of correlation obtains from the standard plot show the linearity of the analytical method. The correlation values of more than 0.99 are evident of the applicability of the analytical method. The calibration curves were obtained in ethanol, pH 6.8, 7.2 & 7.4 buffer solutions. The calibration curves are presented in figures 1-4 along with the equation for regression.



**Figure 1: Calibration curve of Febuxostat in phosphate buffer pH 6.8**



**Figure 2: Calibration curve of Febuxostat in phosphate buffer pH 7.2**

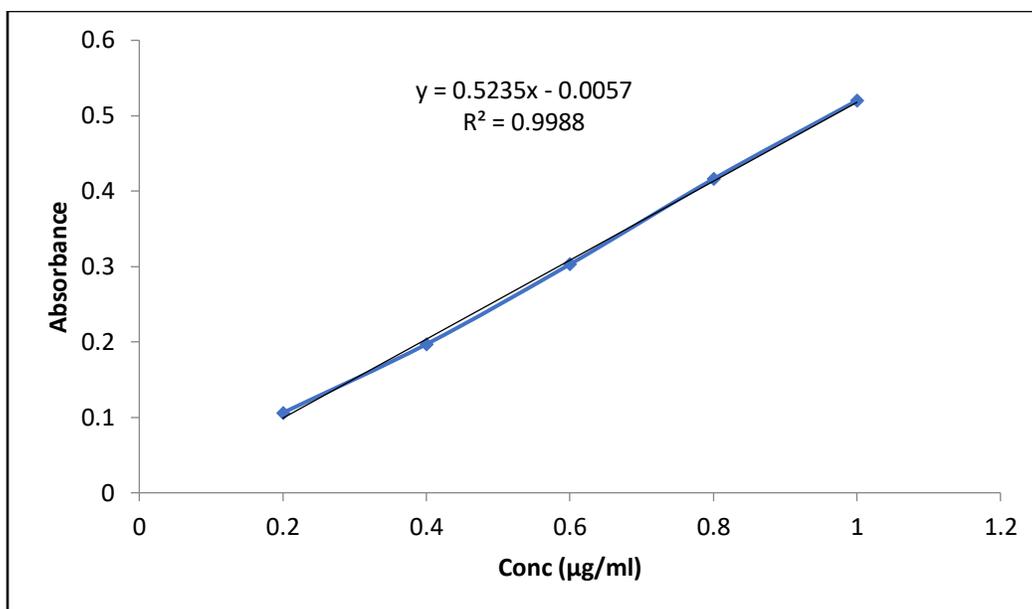


Figure 3: Calibration curve of Febuxostat in phosphate buffer pH 7.4

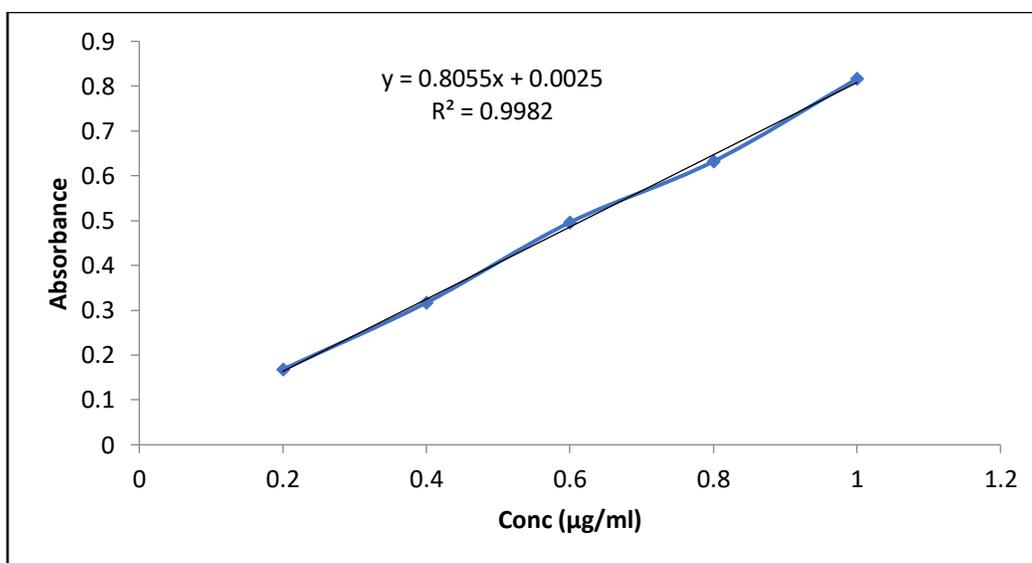
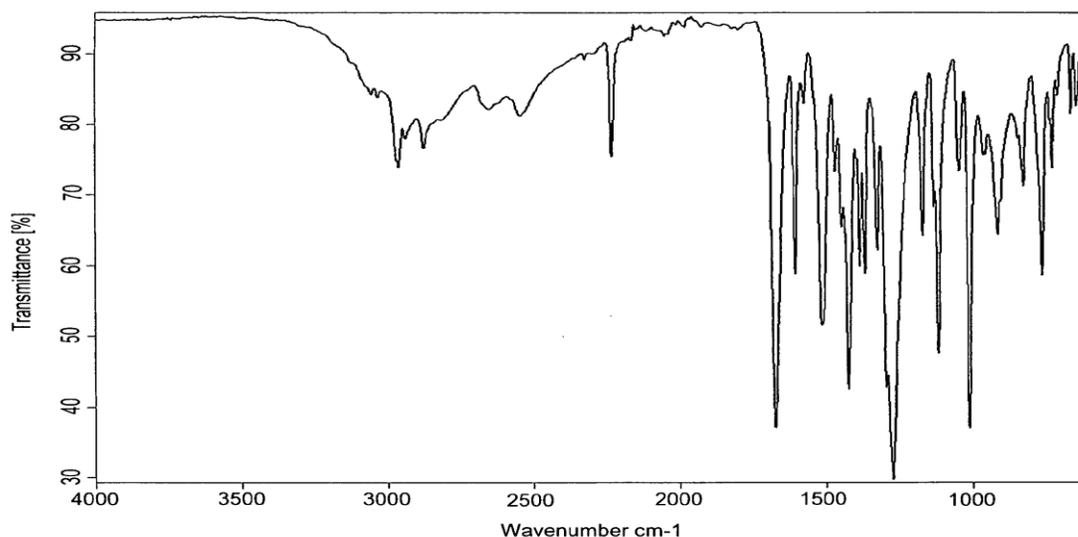


Figure 4: Standard Curve of Febuxostat in ethanol

#### Interpretation of FTIR of Febuxostat:

The FTIR spectrum (figure 5) of the drug was registered in the range of 400-4000  $\text{cm}^{-1}$  and the functional groups present in the compound were determined according to their stretching vibrations. The IR of febuxostat showed a band at 3100  $\text{cm}^{-1}$ , presenting the OH stretching of carboxylic group, the C=O stretch of carboxylic group (COO) appears at 1670  $\text{cm}^{-1}$ , and the band of C-S appears at 1286  $\text{cm}^{-1}$ . The band that appeared at around 2200  $\text{cm}^{-1}$  represents CN.



**Figure 5: FTIR spectrum of Febuxostat**

**Evaluation of Transdermal Patches:**

**Physicochemical Parameters of Transdermal Patches:**

The evaluation of the patch was performed as per guidelines and the result is reported in table 5.

**Table 5: Physicochemical Parameters of Transdermal Patches**

Formulation	Weight Variation (%)	Thickness (mm)	Folding Endurance*	% Drug Content	% Moisture loss	% Moisture uptake
FTDP1	1.016±0.083	0.17±0.06	497.4±23.90	84.2±4.62	7.6±2.18	4.8±1.16
FTDP2	1.048±0.041	0.19±0.05	513.6±18.62	87.5±3.21	7.8±0.95	5.3±1.21
FTDP3	0.926±0.051	0.21±0.08	607.2±38.84	90.16±3.25	7.9±0.96	5.2±0.25
FTDP4	0.938±0.036	0.24±0.03	624.2±61.92	83.66±3.42	8.1±1.65	6.2±0.51
FTDP5	0.982±0.059	0.27±0.08	575.60±28.39	79.0±3.57	9.2±1.96	5.9±0.79

Values are mean ± SD of either 3 or 5\* replicates

The results show that increasing the concentration of sodium alginate causes an increase in the thickness of the patches. The weight variation was found to be around 1% for all the formulations irrespective of the polymer ratios. The folding endurance was lower for lower concentration of sodium alginate but contrastingly an 8:2 ratio of sodium alginate-ethyl cellulose exhibited lower folding endurance compared to 6:4 ratio of the polymers.

***In vitro* release study:**

Release studies are performed for prediction of the reproducibility of rate and time duration of drug release. The importance of polymer dissolution on drug release from matrices has been proven to be ensuring the performance sustained release formulation. Permeation profile of Febuxostat in transdermal patch is shown in table 5.5. The diffusion kinetics of the drug Febuxostat was assessed by graphical method for Zero order, First order, Higuchi and Peppas equation. The R<sup>2</sup> value of model reveals the drug release kinetics of formulations (Table 6).

**Table 6: *In vitro* drug release of formulations**

Formulation	Time (h)	Drug Release ( $\mu\text{g/mL}$ )	Cumulative drug release ( $\mu\text{g/mL}$ )	% CDR	CDR ( $\mu\text{g/cm}^2$ )	Flux ( $\mu\text{g/cm}^2/\text{min}$ )
FTDP1	1	160.88	9652.72	24.13	15082.38	251.37
	2	181.89	11074.35	27.69	17303.67	288.39
	3	307.24	18777.15	46.94	29339.30	488.99
	4	354.42	21915.34	54.79	34242.72	570.71
	5	482.92	29979.79	74.95	46843.42	780.72
	10	582.13	36415.15	91.04	56898.67	948.31
	24	582.13	36997.28	92.49	57808.25	963.47
FTDP2	1	141.78	8506.59	21.27	13291.55	221.53
	2	149.42	9106.82	22.77	14229.41	237.16
	3	322.52	19642.48	49.11	30691.38	511.52
	4	373.52	23025.18	57.56	35976.84	599.61
	5	502.41	31131.65	77.83	48643.21	810.72
	10	602.86	37660.99	94.15	58845.30	980.76
	24	602.86	38263.85	95.66	59787.26	996.45
FTDP3	1	84.47	5068.19	12.67	7919.05	131.98
	2	143.69	8705.67	21.76	13602.61	226.71
	3	153.62	9445.35	23.61	14758.36	245.97
	4	158.11	9868.31	24.67	15419.23	256.99
	5	160.97	10198.34	25.50	15934.90	265.58
	10	244.18	15351.86	38.38	23987.29	399.79
	24	274.27	17401.20	43.50	27189.38	453.16
FTDP4	1	65.37	3922.06	9.81	6128.22	102.14
	2	86.38	5248.18	13.12	8200.27	136.67
	3	115.42	7076.68	17.69	11057.31	184.29
	4	119.90	7461.43	18.65	11658.49	194.31
	5	122.77	7753.26	19.38	12114.46	201.91
	10	192.18	12040.50	30.10	18813.28	313.55
	24	206.50	13092.27	32.73	20456.68	340.94
FTDP5	1	46.27	2775.93	6.94	4337.39	72.29
	2	48.18	2936.81	7.34	4588.77	76.48
	3	58.11	3580.97	8.95	5595.27	93.25
	4	62.60	3908.42	9.77	6106.91	101.78
	5	84.57	5289.07	13.22	8264.18	137.74
	10	163.52	10111.17	25.28	15798.71	263.31
	24	173.27	10859.23	27.15	16967.54	282.79

The results reveal that the formulations that contained higher concentrations of sodium alginate (FTDP 3, 4 and 5) were able to produce a sustained release of the drug from the patches but could not attain complete release of drug over a period of 24 h whereas the formulations with low concentration of sodium alginate (FTDP1 and 2) produced a break release of around 50% drug in first 4 hours and attained almost complete release over 10 h duration. Haque et al<sup>47</sup> reported a very similar release pattern using 1, 1.5, 2 and 2.5% sodium alginate in their formulations.

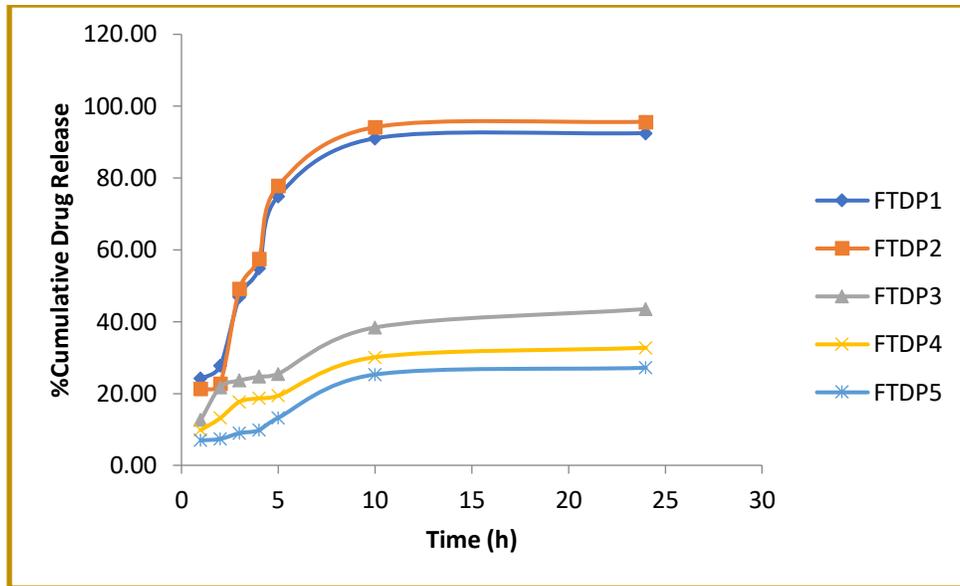


Figure 6: Zero order plot of formulations

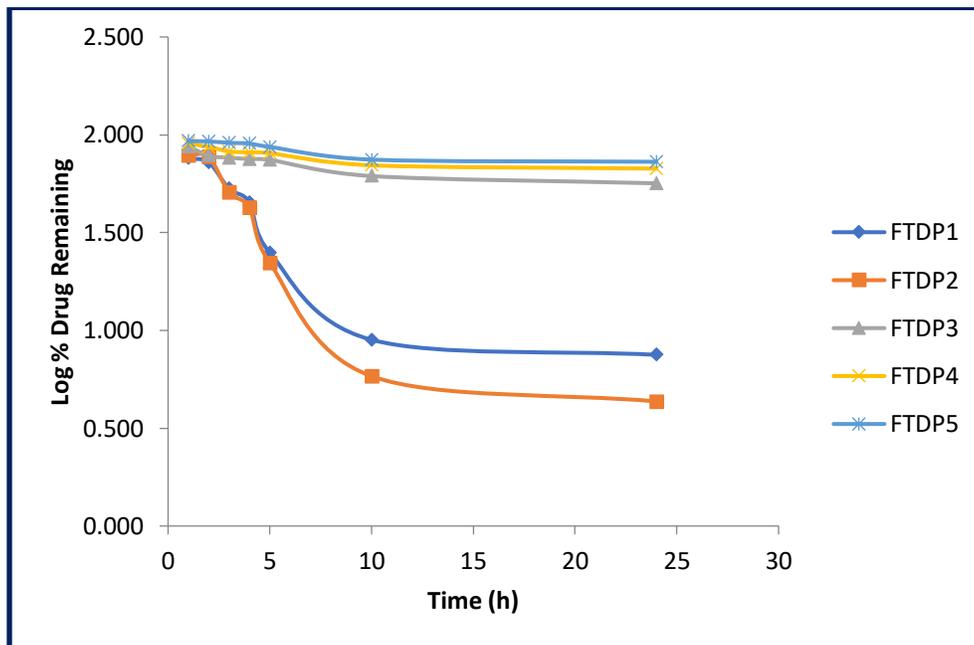


Figure 7: First order plot of formulations

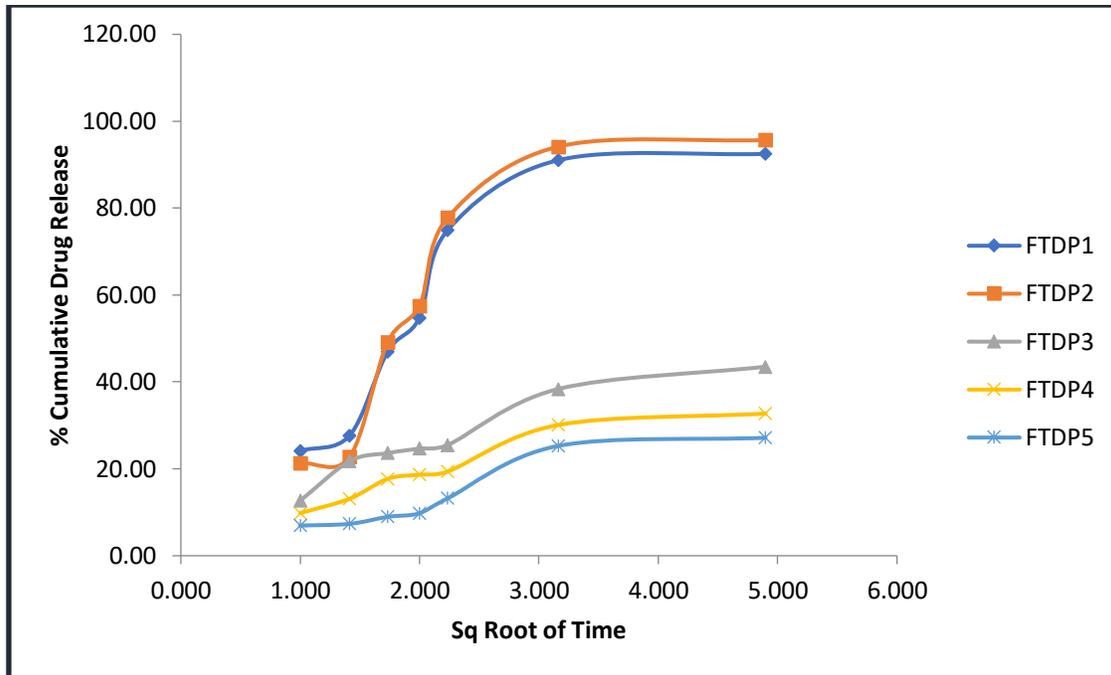


Figure 8: Higuchi's plot of formulations

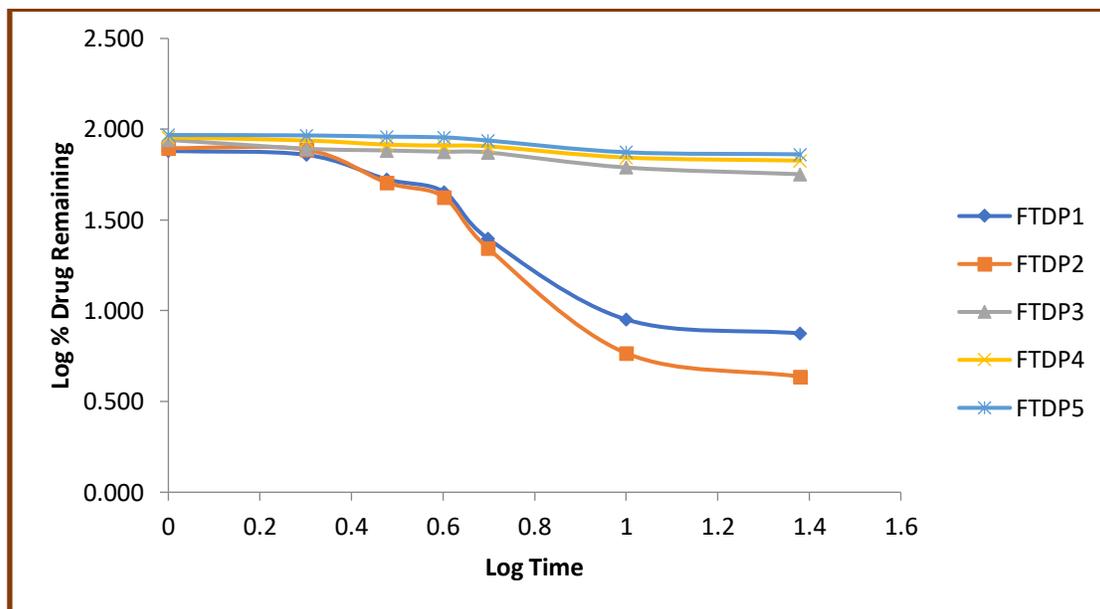


Figure 9: Peppas plot of formulations

Table 7: Drug released kinetic model report

Formulation Code	Zero order R <sup>2</sup>	First order R <sup>2</sup>	Higuchi's model R <sup>2</sup>	Peppas model R <sup>2</sup>
FTDP1	0.6084	0.778	0.7689	0.8976
FTDP2	0.5833	0.7552	0.7466	0.8941
FTDP3	0.7999	0.837	0.9121	0.9523
FTDP4	0.7764	0.7999	0.9005	0.9497
FTDP5	0.7942	0.8016	0.8768	0.8471

From the above table it can be concluded that the formulations are following mixed order kinetics. The best fitting model (Peppas model) exhibits a non-fickian diffusion or anomalous diffusion which depends on erosion-controlled release and diffusion release rate together.

#### CONCLUSION:

In the recent years systemic delivery through skin has grabbed lot of interest. Hence in the current investigation an endeavour was made to formulate Febuxostat as transdermal patches for the management of uric acid levels gout. The patches were smooth, aptly thick and were able to provide a prolonged release of drug for more than time duration of 24 h by changing the concentration of the polymeric matrix. The results of release kinetic study exhibited that the patch FTDP3 was best amongst the others as they were quite stable physically and exhibited a release of around 43% drug over time duration of 24 h. Furthermore the *in vivo* studies need to be pursued to correlate the data obtained from the *in vitro* release studies in order to develop suitable transdermal patches of Febuxostat.

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