Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Research Article

Preparation and Evaluation of Febuxostat Transfersomal Transdermal Drug Delivery System

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ARTICLE DETAILS

Article history:
Received on 12 June 2023
Modified on 22 June 2023
Accepted on 26 June 2023

Keywords:
Febuxostat,
Transfersomes,
Franz Diffusion Cell,
Carbopol 934,
Zero Order Kinetics,
Zeta Potential,
Gout,
Stability Study.

ABSTRACT

Transdermal drug delivery systems are discrete, self-contained dosage forms that release drugs to the bloodstream at a controlled rate through the skin. By incorporating the drug (Febuxostat) into Transfersomal gel using the thin film hydration process with various polymer concentrations, it is possible to increase entrapment effectiveness and drug penetration. As the study mentioned preparation of Transfersomes by using Different ratios of Soya lecithin and Non-ionic surfactant (Span 60 and Tween 20). Transfersomal dispersion then incorporated into gelling agent Carbopol 934 to make Transfersomal Gel. The Drug and excipient study performed by FTIR and revealed that they are compatible with each other. Out of all the batches F4 proved to be optimized batch because of highest entrapment efficiency which was found to be 92.70%. Zeta potential and PDI was -39.7mV and 260.3nm respectively. Optimized Transfersome batch (F4) and Carbopol 934 Gelling agent was used to prepare Transfersomal Gel. The viscosity and spreadability of different concentration of Gelling agent was done. *In vitro* drug release of F4TG4 was found to be highest release than other three batches. Based on our kinetics study the results revealed that all formulations were best fitted in Zero order release kinetic model. The stability study was performed as per ICH guidelines. Our research indicates that the Transfersomal formulation offered a sustained and longer medication delivery with increased bioavailability and better patient compliance. The transdermal route of the transfersomal formulation may be an effective dose form to lessen the unfavourable side effects of the oral route.

INTRODUCTION

Monosodium urate crystals (MSU) accumulate in tissues as a result of the systemic illness gout. Increase in serum uric acid (SUA) levels over the necessary threshold, which results in the formation of uric acid crystals. Gout is first described as an acute joint inflammation that is quickly treated with NSAIDs or colchicine. Renal stones and tophi have recently developed. Dietary changes result in SUA levels falling below the threshold. By utilising the major gout therapy medication, which lowers SUA and dissolves MSU crystals, one can avoid subsequent episodes [1]. Males are more likely to develop hyperuricemia than females, but the risk of gouty arthritis is nearly equivalent for both sexes at any given SUA concentration.

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Gout strikes older postmenopausal women just as commonly as it strikes men. When uric acid levels exceed the solubility limit, which is 6.7–7 mg/dl at physiological pH, crystals may develop in tissues and joints [2].

Recently, there has been an increase in interest in developing novel drug delivery systems for therapeutic substances that are currently on the market. Due to the development of a novel delivery mechanism, the performance of existing drug molecules in terms of safety and efficacy, as well as patient adherence, has greatly improved, which has also raised the drug's overall therapeutic benefit [3]. The transdermal drug administration system is a popular way to take medications (TDDS). Transdermal drug delivery systems (TDDS) are discrete, self-contained dosage forms that, when applied to healthy skin, release drugs to the bloodstream at a controlled

rate through the skin. TDDS are dose forms designed to apply a therapeutically effective amount of medication to the patient's skin [4]. One of the most recent developments in drug administration is transdermal distribution, which only needs to be applied lightly once. It is convenient, improves patient compliance, and prevents the negative side effects of a drug caused by a temporary overdose. Transdermal medicine delivery methods have been proven to be both safe and efficient. Highly accomplished scientists all over the world are making advantage of their potential for controlled release [5]. The trans epidermal and trans follicular pathways are two potential routes for drug penetration through intact skin, and they are depicted. The trans epidermal pathway's multi-layered, multicellular barrier allows molecules to penetrate through the stratum corneum. Intracellular or intercellular trans epidermal penetration are the two types. Molecules are transported via the trans follicular pathway through the sweat glands and hair follicles [6].

The formulations, techniques, and technologies known as novel drug delivery systems are used to safely distribute pharmaceutical components to the body as needed to accomplish their desired therapeutic effects (NDDS). The use of a drug in a dosage form or in a device that releases the drug from a single application at a predetermined rate, at a predetermined location, and over an extended period of time is part of a therapeutic system known as an innovative drug delivery system [7]. Hydrophilic, charged hydrophilic, lipophilic, and amphiphilic medications can all be delivered by these vesicles. While lipophilic, amphiphilic, and charged hydrophilic drug molecules can be associated with the bilayers of the vesicles, hydrophilic drug molecules can only be trapped in the watery compartment of vesicles [8].

Tranfersomes is The Latin word "Transferre", which means "carrying body" and "to carry over", and the Greek word "soma", which means "a body", are the roots of the word "Tranfersome". In 1991, Gregor Cevec created Tranfersome. A composite lipid bilayer that is both ultra-deformable and incredibly flexible as well as stress-responsive surrounds the aqueous centre of the complicated system known as a Transfersome [9]. Tranfersomes break through the skin's barrier to penetration by pressing along the stratum corneum's internal sealing lipid. The right mixture of surface-active chemicals in the right proportions produces flexible Transfersome membranes [10]. The mechanism action of Tranfersomes is break through the stratum corneum's internal sealing lipids to penetrate the skin's barrier [11]. It penetrates the skin barrier when applied to the non-occluded skin surface, reaching the deeper strata (a region rich in water) to hydrate them. The next step is to use natural trans epidermal activity to dry lipid vesicles inside the stratum corneum in order to reach the deeper epidermal layer. As a result, Transfersome uptake is influenced by the moisture gradient that exists across the epidermis, stratum corneum, and surrounding environment [12].

According to our research, these structures have a bi-layered architecture that allows them to enclose a range of pharmacological classes. Due to its advantages, transdermal medication administration techniques have had a big impact lately. These techniques are often used in the treatment of diabetes and other chronic disorders. The aspect of transdermal drug delivery that generates the most issues is the barrier function of the top layer of skin [13]. A few numbers of high-molecular-weight chemicals may be delivered safely through the skin because they cannot pass through skin. The use of Tranfersomes to encapsulate pharmaceuticals is one of the most promising answers to this problem [14].

A novel, powerful, non-purine-selective xanthine oxidase inhibitor called febuxostat has the potential to block XO in both its oxidised and reduced forms. The treatment choices for urate-lowering therapy in gout patients can be expanded by febuxostat. Due to its low pH (pKa 14 3.08), it is essentially insoluble in water. Its oral bioavailability is impacted by its decreased water solubility and susceptibility to enzymatic breakdown in the stomach and liver, and the presence of food also reduces its Cmax by 38–39%. For these reasons, the transdermal route is favoured for its administration. The goal of the current study was to develop and evaluate the *in vivo* efficacy of a febuxostat-containing transfersomal gel. By using different ratios of the surfactants Tween 20, Span 60, and soya lecithin, transfersomal formulations were created and then incorporate into Carbopol 934. They were then tested for *In-Vitro* properties, stability studies.

MATERIALS AND METHODS

Materials

Febuxostat was purchased from pharmaceutical company (Precise Chemi Pharma, Ltd. Navi Mumbai). Soya Lecithin, Tween 20, Span 60 and Carbopol 934 were obtained from Research-Lab Fine Chem Industries, Mumbai. propylene glycol, glycerol, methanol, sodium chloride, Potassium phosphate (Monobasic), Sodium Phosphate (dibasic), triethanolamine was purchased from Research- Lab Fine Chem Industries, Mumbai.

Methodology

Ultraviolet Visible (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. Spectrophotometric scanning and determination of λmax of drug was done. From the standard stock solution, 1 mL was pipetted out and diluted up to 10 mL using methanol and it was scanned between wavelength 200 nm to 400 nm. For Plotting of calibration curve of Febuxostat From the standard stock solution, series of dilution were made by pipetting out 0.2, 0.4, 0.6, 0.8, 1.0 and 1.2 mL of standard stock solution and diluting up to 10 mL by methanol in order to obtain 2, 4, 6, 8, 10 and 12 ppm solution respectively. Absorbance was measured at 315 nm by using UV-Vis Spectrophotometer. This experiment was performed in triplicate and calibration curve was plotted in order to check the linearity [15].

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 excipients, as well as mixtures of the two, were recorded by FTIR.

Preparation of Transfersomes by Thin Film Hydration Method

Utilizing febuxostat, soy-lecithin, Span 60, and Tween 20, transfersomal formulations were made using the thin film hydration technique. The medication, phospholipid, and surfactant were weighed and completely dissolved in organic solvents before being put to a clean, dry round-bottom flask (methanol: ethanol). The solvent was evaporated for 30 to 40 minutes at reduced pressure and 60 revolutions per minute above the lipid transition temperature using a rotary flash evaporator. After being hydrated for an hour at 60 rpm with PBS, the resulting thin lipid layer was retained overnight for hydration (pH 7.4). When the dry layer was hydrated using aqueous media such phosphate buffered saline (PBS) pH 7.4 with gentle shaking, a transfersomal dispersion comprising multi-lamellar vesicles was created. Using aqueous media, such as phosphate buffered saline (PBS), pH 7.4, and gentle shaking at 60°C temperature for roughly an hour, the dry layer was hydrated. The dispersion-containing vesicle was kept refrigerated for a further 24 hours [16]. Formulation batches are described in Table 1.

Separation of Unentrapped Material Centrifugation

Dispersion is separated from undesirable material and free, unentrapped drugs by centrifugation. The supernatant solution was separated after centrifuging the transfersomal suspension at 6000 rpm. The pellet is separated, cleaned, and then resuspended to create a transfersomal suspension devoid of the unentrapped drug [17].

Table 1: Formulation of Transfersomal Dispersion (F1 to F8)

Formulation Code	Drug	Soya-Lecithin	Span 60	Tween 20
F1	40mg	0.90%	0.10%	-
F2	40mg	0.85%	0.15%	-
F3	40mg	0.80%	0.20%	-
F4	40mg	0.75%	0.25%	-
F5	40mg	0.90%	-	0.10%
F6	40mg	0.85%	-	0.15%
F7	40mg	0.80%	-	0.20%
F8	40mg	0.75%	-	0.25%

Optimization of Tranfersomes

Visual inspection was done by putting the transfersomal dispersion in clear containers; turbidity, flocculation, and sedimentation were also examined. Vesicle size and zeta potential of dispersion was determined by SZ- 100 nanoparticle instrument. Transmission electron microscopy (TEM) was utilised to see the vesicles. Surface morphology was studied using scanning electron microscopy (SEM), although TEM offers a better level of resolution; using a digital pH metre that had been previously calibrated by standard solutions with pH of 4, 7, and 9.2, respectively [18].

Entrapment Efficiency

Centrifuging the transfersomal dispersion at 15000 rpm for 30 minutes for the purpose of calculating the percent of unentrapped drug, supernatant liquid was used. The determination was made using a UV spectrophotometer [17]. The percentage of entrapment effectiveness was determined using:

% Entrapment efficiency = % Initial drug quantity −% unentrapped drug

Preparation of Transfersomal Gel by Dispersion Method

The optimum Transfersome formulation was chosen to be added to the gel base produced with different Carbopol 934 concentrations. While stirring continually, Carbopol 934 was weighed out and placed on top of the distilled water. It was submerged for two hours while being irrigated. The required quantity of the best Tranfersomes formulation was added, and then other substances like propylene glycol (10% w/w) and glycerol (30% w/w) were continually swirled and dispersed. The gel was neutralised with triethanolamine (TEA) to a pH of 7.4, and the final weight was adjusted with distilled water. The gel was left undisturbed overnight after being sonicated for 30 minutes on a bath sonicator to remove trapped air [19]. Formulation batches of Carbopol 934 gel with various concentration are described in Table 2.

Table 2: Formulation of Carbopol 934 febuxostat transfersomal gel

Formulation codes	Transfersomes containing Febuxostat	Carbopol 934	Propylene Glycol	Glycerol
F4TG1	1%	0.5%	10%	30%
F4TG2	1%	1%	10%	30%
F4TG3	1%	1.5%	10%	30%
F4TG4	1%	2%	10%	30%

Evaluation of Transfersomal Gel

Visual inspection was used to check the homogeneity of transfersomal gels that had been placed in a clear beaker. Grittiness were examined under microscope. Using a digital pH metre that had been previously calibrated with standard solutions with pH values of 4, 7 and 9.2, respectively, the pH of the transfersomal gels was assessed. The viscosity of the transfersomal gels was determined by Brookfield viscometer DV2T-E95 rotated at 5 rpm for 5 min at 25°C temperature. Using equipment suggested by Mutimer et.al (1956) that was appropriately adjusted in the lab, the spreadability of transfersomal gels was assessed [20].

Drug Content (%)

A 100 mL volumetric flask was filled with solvent after one gram of the freshly made gel was added to it. The dispersion was sonicated in order to rupture the vesicles. The dispersion may have been diluted much more by filtering it. The drug content was assessed utilising a linear regression analysis method at a 315 nm wavelength.

***In-Vitro* Diffusion Study**

An *In-Vitro* diffusion study of Transfersomal gels was carried out by using a set of Franz diffusion cells, to study the release rate of drug from formulation. The receptor chamber was filled with receptor medium (PBS pH 7.4). Running water through a jacket that covers the cell body kept the temperature of the receptor media at 37°C plus or minus 1°C throughout the experiment. After being soaked in receptor medium for 12 h, a dialysis membrane was clamped between two chambers. 1g of the formulation was administered to the donor cell. 1 mL samples of the receptor cell were then taken after a predetermined period of time. To keep the volume constant, an equal amount of new medium was added after each collection. Fresh receptor media was used as the blank for the spectrophotometric examination, and the extracted samples were diluted as necessary. An equation created from standard calibration was used to calculate the drug concentration delivered at a specific time interval [19].

Drug Release Kinetic Model

The kinetic models, in which the amount of medication that dissolves (Q) are a function of the test time (t) or of (t), can be used to explain how the drug dissolves from the novel dosage forms. Commonly used analytical definitions of the Qt include the Higuchi-matrix, Peppas-Korsmeyer model, zero order definition, and first order definition [13].

Stability Study

The stability analysis of the formulation was finished in accordance with the demands of the International Council for Harmonization (ICH). Freshly manufactured formulations were divided into groups and stored in accordance with ICH regulations. Periodically, samples were extracted and examined for the numerous evaluation factors mentioned above. The evaluation parameters must remain constant throughout time and under the necessary storage conditions for a formulation to be considered stable.

RESULT AND DISCUSSION

RESULT

Ultraviolet Visible (UV-Vis) Spectrophotometry

The greatest peak in the UV-Vis spectrum analysis of febuxostat, which is regarded as the drug maximum absorbance (max), was observed at 315 nm. The value of R^2 was found to be 0.998 indicating the relation of drug concentration and absorbance was linear in the selected range. The absorbance of different concentrations of drug in methanol and the standard calibration curve is represented the equation y = 0.058x+0.005; where y is absorbance and x are concentration. UV spectra and Calibration curve of febuxostat in methanol was shown in Fig. 1 respectively.

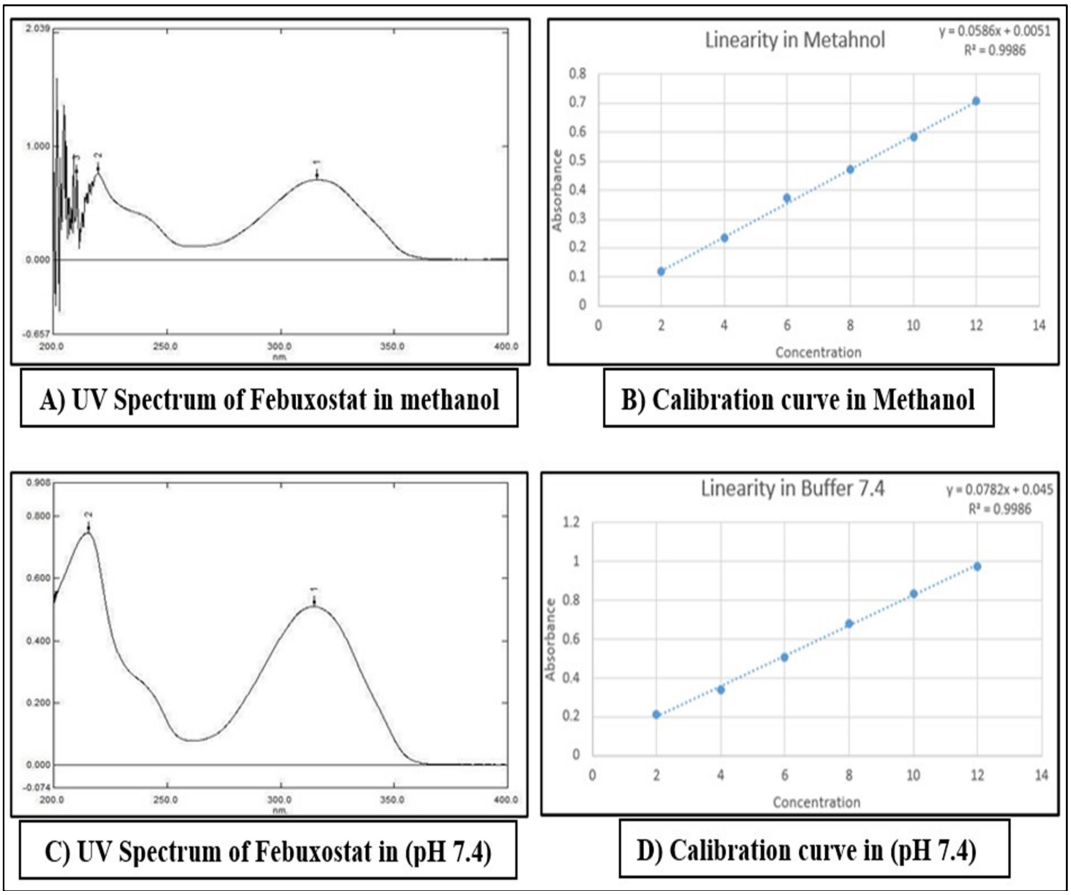

Figure 1: UV spectrum and calibration curve of Febuxostat

A) UV absorption spectra of drug in methanol show that the λ max was observed to be at 315 nm. This confirms the drug to be pure. B) The value of R^2 was found to be 0.9986 indicating the relation of drug concentration and absorbance was linear in the selected range.C) UV absorption spectra of drug in methanol shows that the λ max was observed to be at 315 nm. This confirms the drug to be pure. D) The value of R^2 was found to be 0.9986 indicating the relation of drug concentration and absorbance was linear in the selected range.

The concentration from 2 ppm to 10 ppm of febuxostat in phosphate buffer solution pH 7.4 was selected for calibration curve. The value of R^2 was found to be 0.998 indicating the relation of drug concentration and absorbance was linear in the selected range. The absorbance of different concentrations of drug in phosphate buffer solution pH 7.4 and the standard calibration curve is represented the equation y = 0.078x + 0.045; where y is absorbance and x are concentration. UV spectra and calibration curve of febuxostat in methanol was shown in Fig. 1 respectively. UV spectra and calibration curve of febuxostat in phosphate buffer solution pH 7.4 was shown in Fig. 1 respectively.

Drug – Excipient Compatibility Study by Fourier Transform Infra-Red (FTIR) Spectroscopy

IR spectrum of pure drug and excipients along with the mixture of drug and excipients were recorded by FTIR and the compatibility of drug and excipients was checked by comparing the spectra. The FTIR spectra of Febuxostat and Excipient mixtures are shown in Fig. 2. The spectrum of pure drug presented characteristic bands at 655.80, 715.59, 775.38 and 806.25 cm^{-1} for C-Cl Group. For C-N group peaks noted on 914.26 and 952.84 cm^{-1}. Alcohol group showing peak on 1006.84, 1114.86, 1174.65 cm^{-1}. Ester, ether, carboxylic acid and amide group type of vibration with frequency 1217.08, 1276.88, 1384.89, 1600.92, 1683.86 cm^{-1}. For C=C group peak noted on 1409.96, 1512.19, 1600.92 cm^{-1}. Nitriles and amines Group type of vibrations with frequency 2245.50 and 3169.04 cm^{-1}. The spectrum of febuxostat and excipients mixtures presented bands at 653.87, 715.59, 775.38, 914.26, 954.76 cm^{-1} for alkenes and aromatics. For alcohols, ethers, esters, carboxylic acids and amides groups showing peaks on 1016.49, 1112.93, 1172.72, 1217.08, 1276.88 cm^{-1}. C=C group type of vibration with frequency 1514.12, 1602.85 cm^{-1}. For C-H and O-H group 2862.36, 2922.16, 3172.90 cm^{-1} are noted.

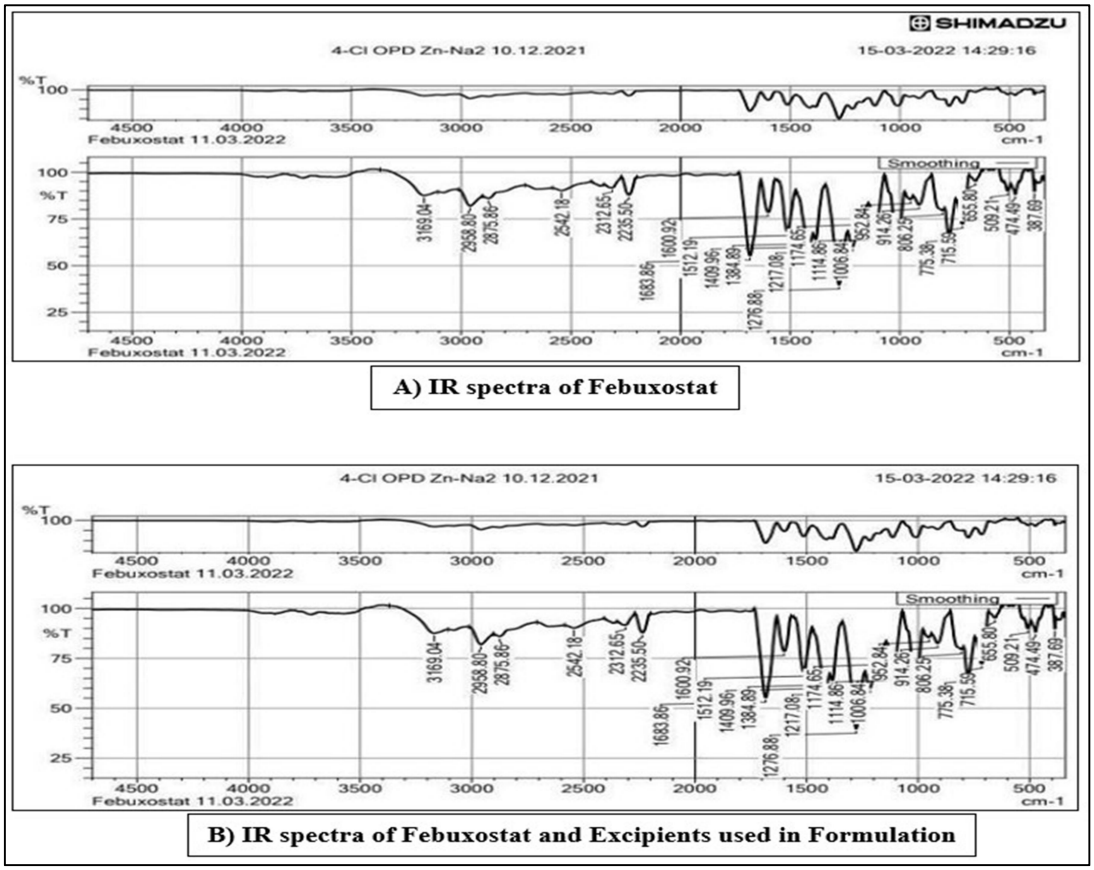

Figure 2: FT-IR Spectroscopy of Febuxostat drug and with Excipients product
A) The observed peaks of Febuxostat were found to be in the range which confirmed that the drug was pure. B) The observed peaks of Drug and Excipients mixture indicate that Excipients are compatible with Drug.

Entrapment Efficiency of Transfersomes

The entrapment efficiency for all the 8 formulations was evaluated and it varied between 71.92% to 92.70% Among all the 8 formulations the highest entrapment efficiency was found to be for span 60 (F4) of 0.25% of concentration with soya lecithin 0.75% concentration with entrapment of 92.70% followed by tween 20 (F6) with the entrapment efficiency of 71.92 %. It shows that Span 60 has great entrapment efficiency than tween 20. As the concentration of span 60 increases entrapment efficiency also increases. It is also same in the case of Tween 20. All entrapment efficiency percentage shown in tabulated form in Table 3.

Table 3: Entrapment efficiency of febuxostat Transfersomes

Sr. No	Formulation	Entrapment Efficiency (%)
1	F1	83.19
2	F2	84.485
3	F3	86.295
4	F4	92.707
5	F5	72.16
6	F6	71.38
7	F7	76.125
8	F8	79.225

*n (number of observations) = 03

Electron Microscopy

Transmission Electron Microscope (TEM) images of the F4 formulation shows the formation of discrete spherical uniform uni-lamellar vesicles. The average size of Transfersome was found to be 200 nm. TEM images are shown in Fig. 3.

Zeta Potential Measurement

Zeta potential gives an idea about stability of the sample, hence shortens stability testing, thereby reducing the cost and obviously the time of testing. Zeta potential of the F4 formulation was determined by using zeta-sizer. The value of zeta potential was found to be -39.7mV this indicates good stability thereby better shelf-life. Poly dispersity index of optimized batch was found to be 0.443 and average size was 260.3 nm. The vesicle size, distribution and zeta potential of the optimized formulation (F4) was determined by third party lab. The observed graph of zeta potential is shown in Fig. 4.

Viscosity and Spread Ability of Transfersomal Gel

F4TG2 and F4TG3 were found to have appropriate viscosity suitable for topical application. F4TG4 was slightly more viscous. Viscosity of F4TG1was found to be very low. Spreadability of F4TG1 and F4TG2 was found to be good as compared F4TG3 and F4TG4. 2% febuxostat transfersomal gel shows best viscosity so it concluded that as the concentration of gelling agent is increases, Viscosity also increases. In case of spreadability, Gelling agent concentration is inversely proportion to Spreadability. Observation of viscosity and spreadability is shown in Table 4.

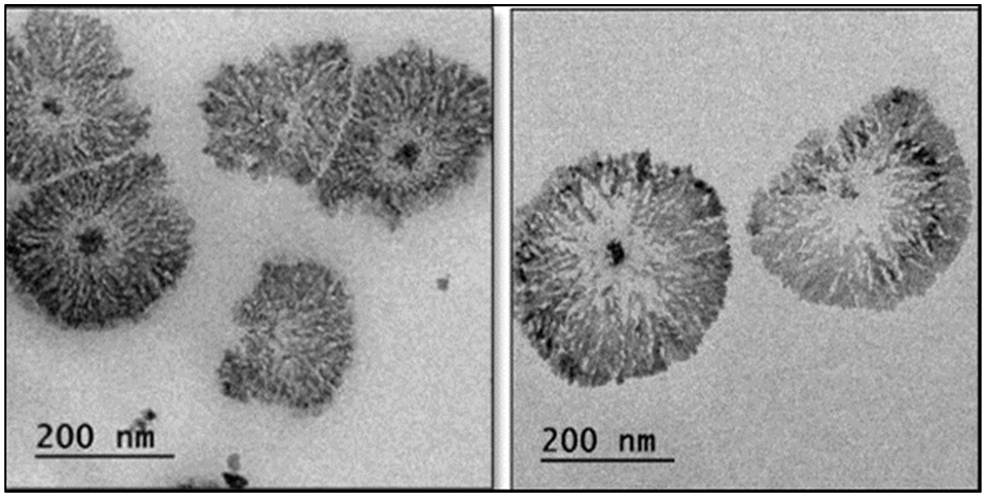

Figure 3: TEM images of Febuxostat Transfersomes
Transfersomes shows the formation of discrete spherical uniform uni-lamellar vesicles and shows average size 200 nm.

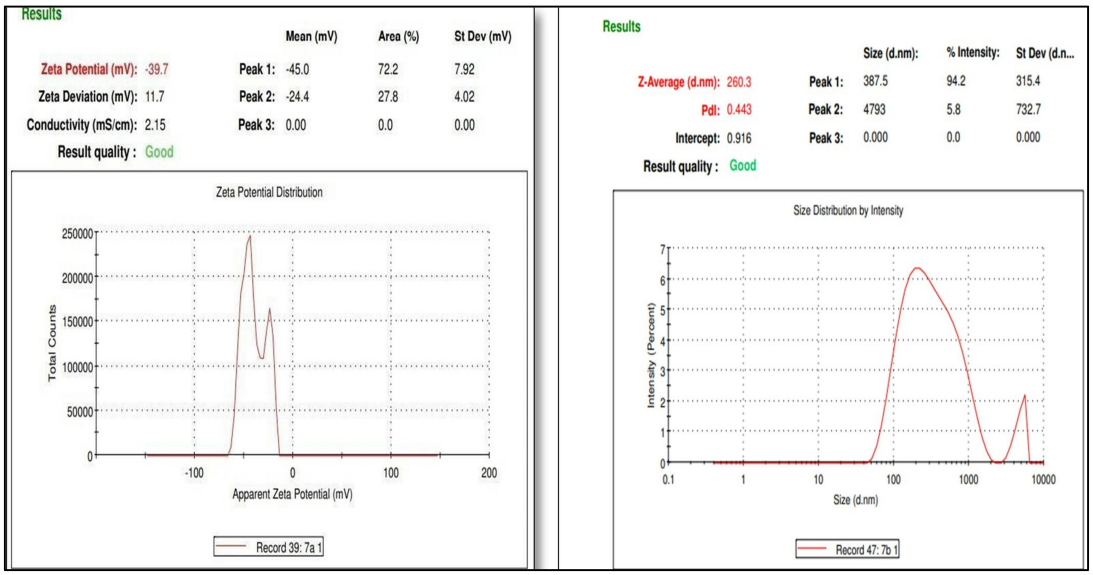

Figure 4: Zeta potential Measurement of Febuxostat Transfersomes

The value of zeta potential was found to be -39.7mV this indicates good stability thereby better shelf-life. The value of PDI 0.443 and Average size is 260.3 nm.

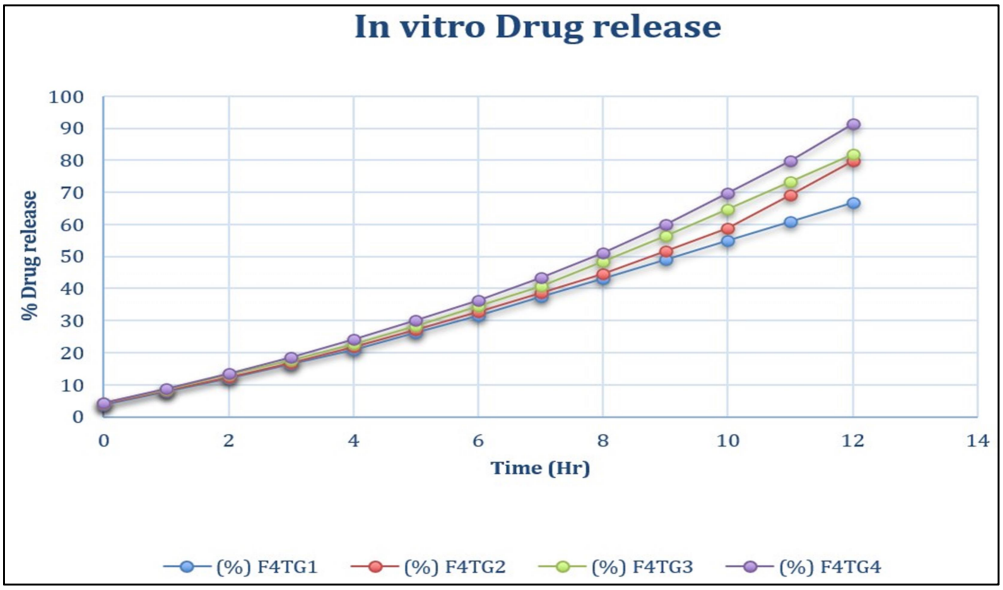

Figure 5: *In vitro* Diffusion study of Febuxostat Transfersomal Gel (F4TG1 to F4TG4)

Above figure shows *In vitro* Drug release of various concentration of Carbopol 934 Gel in 12 hrs. F4TG4 (2%) shows better % Drug release.

Table 4: Evaluation of Febuxostat transfersomal gel

Batch	Viscosity (cP)	Spreadability (g.cm/sec)	Drug content uniformity (%)	Extrudability
F4TG1	33,720	172.9± 5.93	83.26	98 ± 0.41
F4TG2	41,480	159± 5.44	84.21	94 ± 0.78
F4TG3	49,530	88.7±4.89	85.29	86 ± 0.32
F4TG4	52,560	55.8±4.17	89.31	80 ± 0.85

Drug Content Uniformity and Extrudability

Drug content uniformity of F4TG4 was found to be best representing homogeneous distribution of drug (entrapped in Transfersomes) throughout the gel. Drug content uniformity range lies between 83.26 to 89.31%. 2%

Transfersomal gel showed highest % drug content uniformity i.e., 89.31. More quantity of Transfersomal gel extruded indicates better extrudability. Extrudability of F4TG1 and F4TG2 was found better as compared to other formulations. Observed value shown in Table 4.

In Vitro Diffusion Study

In vitro drug diffusion studies were performed using Franz diffusion cell to determine the sustained release nature of the formulations. The diffusion study was continued up to 12 hours, whereas the other formulations were sustained up to 8 -11 hours. F4TG4 shows 91.25% drug release in 12 hrs. The order of *in vitro* controlled drug release up to 12 hours, F4TG4 > F4TG3 > F4TG2 > F4TG1.This are show in Table 5 and Fig. 5.

Drug Release Kinetic Modelling

The *in-vitro* release data was fitted in various release kinetic models to predict the release mechanism of drug from the transfersomal gel. The R^2 values of all formulations were tabulated in Table 6 respectively. Based on our kinetics study the results revealed that all formulations were best fitted in zero order release kinetic model as they shown highest R^2 value among all kinetic models. F4TG4 showed highest R^2 value among all the formulations recommended that best fit in zero order kinetic. It indicates that a constant amount of drug is released per unit time from the transfersomal gel. R^2 values are shown in Table 6.

Stability Study

Periodical assessment of formulation was done for 90 days. Transfersomal gel was found to be opaque, creamish with characteristic odor and particles were absent. pH, viscosity, spreadability and residual drug content at different temperatures i.e., 40°C ± 2°C / 75 % RH ± 5 % RH at was observed and tabulated in Table 7 respectively. All observations were taken in triplicate.

Table 5: *In-Vitro* Diffusion study of Transfersomal gel of Febuxostat

Time (hrs.)	Drug diffused from the Formulation (%)			
	F4TG1	**F4TG2**	**F4TG3**	**F4TG4**
0	3.84	3.97	4.23	4.29
1	7.88	8.14	8.58	8.84
2	12.05	12.43	13.07	13.58
3	16.34	16.85	17.69	18.52
4	20.96	21.66	22.69	24.01
5	26.15	27.05	28.39	30.03
6	31.66	32.82	34.48	36.25
7	37.37	38.66	40.76	43.30
8	43.17	44.69	48.46	51.19
9	49.01	51.55	56.47	59.91
10	54.91	58.85	64.74	69.78
11	60.84	69.11	73.20	79.84
12	66.79	79.94	81.88	91.25

Table 6: Drug release kinetic modelling of febuxostat transfersomal gel

Formulation / Kinetic Model	F4TG1 (0.5%)	F4TG2 (1%)	F4TG3 (1.5%)	F4TG4 (2%)
Zero order model	0.9776	0.9794	0.9844	0.9914
First order model	0.8169	0.7759	0.8609	0.904
Higuchi model	0.8669	0.8539	0.9135	0.9275
Korsmeyer-peppas model	0.952	0.9684	0.9242	0.9021
Hixson-Crowell model	0.9166	0.979	0.9033	0.9334

Table 7: Stability Study of febuxostat transfersomal gel

Formulation	**F4TG4**			
Storage Condition	40°C ± 2°C / 75 % RH ± 5 % RH			
Time interval (days)	0	30	60	90
Homogeneity	+++	+++	+++	+++
Grittiness	+++	+++	+++	+++
pH	7.00±0.06	7.01±0.09	7.12±0.05	7.00±0.08
Viscosity (cP)	52,480	52,480	52,480	52,480
Spreadability (g.cm/sec)	59.8 ± 4.17	58.6 ± 4.15	59.3± 4.07	59.8 ± 4.12
Extrudability (%)	78± 0.85	78± 0.85	78± 0.65	78± 0.83
Drug Content Uniformity	90.32	90.43	90.45	90.44

DISCUSSION

A long-term treatment for gout caused by elevated uric acid levels is febuxostat. It is a nonpurine selective xanthine oxidase inhibitor it inhibits the molybdenum pterin center, the xanthine oxidase active site, non-competitively. After oral administration, 84% of febuxostat is absorbed in gut and highest blood plasma concentrations are reached. Half-life of febuxostat is 5-8 hrs. It's a weak acid (pKa=3.08), it's essentially insoluble in water. Because it is less soluble in water and susceptible to enzymatic degradation in both the intestine and the liver, its oral bioavailability is affected, and the presence of food lowers its Cmax by 38-39 %, transdermal administration is preferable.

In the present work, Soya lecithin and non-ionic surfactants were used to prepare Transfersomes. to prepared transferosmal gel by using various concentration of Carbopol 934. Drug excipients interaction study by FTIR was done according to standard system. It was suggested that there was no physical and synthetic interaction between rug and excipients. UV vis spectra was conducted in solvents like methanol and phosphate buffer solution pH. The standard calibration curve of febuxostat was completed in methanol and phosphate buffer solution 7.4 with better linearity. Febuxostat Transfersomes were prepared. On the basis of highest entrapment efficiency F4 formulation was selected as optimized batch. Entrapment efficiency for all the batches lied in the range of 71.92% to 92.70%. Entrapment efficiency of optimized batch (F4) was found to be 92.70% because of Span 60 low HLB value.

Particle size and poly dispersity index for optimized batch (F4) was found to be 260.3nm and 0.443, respectively. TEM of Transfersome was conducted; average size of vesicle was 200nm. It can be clearly concluded that as the phospholipid concentration decreases and span 60 concentration increases Entrapment efficiency increases. Vesicle membrane permeability is influenced by the surfactants carbon chain length and transition temperature. The ideal amount of surfactant to utilize in the formulation relies on the phospholipids packing density and how they interact with the surfactant. The permeation property of Transfersomes may be affected by the presence of surfactants images revealed vesicular, spherical particle with nm range.

Transfersomal gel of febuxostat was prepared by optimized batch of Transfersomes (F4) using 2% Carbopol 934.The prepared gel was evaluated for its pH, viscosity, spreadability, drug content. Viscosity of gel was found to be in range 33,720 to 52,560. F4TG4 (2%) Batch showed better viscosity than other concentration. In case of spreadability, F4TG4 showed 55.8 g.cm/sec.%. Drug content uniformity range lies between 83.26 to 89.31 %.2% Transfersomal gel showed highest % Drug content uniformity i.e., 89.31. *In vitro* drug release of transfersomal gel batches examined under phosphate buffer solution with pH 7.4 because febuxostat is a weak acid in nature therefore it reached into blood in unionized form.

Diffusion study was observed in 12 hrs in all transfersomal gel concentration. Drug diffused from formulation (%) lies between 66.79 to 91.25 %. 2% Febuxostat transfersomal gel showed highest drug release as the drug was entrapment in vesicle allowing the drug to be release slowly and for longer period of time. Zero order showed better linearity than other kinetic models. Among all formulations F4TG4 shoed better R^2 value. The stability study was done for 90 days with condition 40°C ± 2°C / 75 % RH ± 5 % RH followed by ICH guidelines and it was seen that the best optimized formulation and no significant changes were found in prepared Febuxostat transfersomal gel.

CONCLUSION

A complex system with a highly flexible, highly deformable, and stress-responsive aqueous core called a Transfersome is wrapped by a lipid bilayer. The efficacy and use of transfersomal gel in the transdermal drug delivery method have been established. According to research, it was concluded that transfersomal suspension was prepared by the thin film hydration method, and its TEM, zeta potential, and entrapment effectiveness were assessed. The entrapment efficiency of Span 60 showed 92.707% and Tween 20 showed 79.225%. The average Transfersome size was found to be 200 nm. A febuxostat transfersomal gel was produced by mixing the Transfersomes solution with carbomer gels. Febuxostat 2% transfersomal gel shows the best result in case of Viscosity, Drug content and spreadability. The gel contains 2% Carbopol 934 shows the best and most promising results. A Franz diffusion cell was used to examine the suspensions homogeneity, spreadability, extensibility, drug content, and *In-*

Vitro drug release after it was added to gels with different concentrations. Based on kinetics study the results revealed that all formulations were best fitted in zero order release kinetic model as they have shown highest R^2 value among all kinetic models. The gel contains 2% showed highest R^2 value among all the formulations recommended that best fit in zero order kinetic. The stability study was done for 90 days with condition 40℃ ± 2℃ / 75 % RH ± 5 % RH. Our research indicates that the transfersomal formulation offered a sustained and longer medication delivery with increased bioavailability and better patient compliance. The preparation process is straightforward and practical from an industrial standpoint. Transfersomes may therefore be thought of as an efficient means of delivering febuxostat via transdermal route.

ACKNOWLEDGEMENT

We thank Dr. Ashish Jain (Principal of Shri D.D. Vispute college of Pharmacy and Research centre), for providing his invaluable support. We would also like to thank Mr. Kedar Bavaskar for his assistance. Also big thanks to Precise Chemi Pharma, Ltd. Navi Mumbai for providing with the Gift sample of Febuxostat. The authors are also thankful to Research-Lab Fine Chem Industries, Mumbai for providing various excipients.

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