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DEVELOPMENT AND IN VITRO CHARACTERIZATION OF A TOPICAL FEBUXOSTAT GEL FORMULATION FOR ENHANCED TRANSDERMAL DELIVERY

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ABSTRACT
Transdermal Drug Delivery Systems (TDDS) represent an advanced therapeutic modality, offering controlled and sustained drug release while mitigating the risks associated with systemic fluctuations and adverse effects. This investigation centers on the formulation and comprehensive evaluation of a febuxostat-incorporated topical gel, engineered to optimize transdermal delivery. A nanoemulsion technique was employed to encapsulate febuxostat in varying concentrations, followed by integration into a gel matrix. A series of rigorous physicochemical assessments, including stability profiling, Fourier-transform infrared (FTIR) spectroscopy, zeta potential analysis, spreadability testing, and in vitro drug release studies, were performed to evaluate the characteristics and performance of the formulated system. The findings indicated that the formulations retained physical stability and pH levels within the physiologically acceptable range, while demonstrating efficient and controlled drug release. The results substantiate the potential of the optimized febuxostat-loaded nanoemulsion gel as a promising transdermal delivery vehicle, offering a sustained release profile that enhances therapeutic efficacy and patient compliance.

Keywords: *Transdermal Drug Delivery Systems (TDDS), febuxostat, nanoemulsion, topical gel, sustained release, controlled drug delivery etc.*

I. INTRODUCTION
Rapid advancements in medication management have produced a wide range of medications and traditional forms, such as pills and injections, which frequently cause variable drug levels and possible adverse effects [1], [2]. By reducing systemic peaks, increasing therapeutic efficacy, and providing regulated, continuous release through the skin, transdermal drug delivery methods provide a possible substitute [3], [4].

Transdermal Drug Delivery Systems (TDDS) are separate, self-contained dosage forms intended to administer medications at a regulated pace via the skin and into the bloodstream [5]. They provide a number of benefits, including prolonged drug release, enhanced patient adherence, prevention of hepatic and gastrointestinal first-pass metabolism, and streamlined dosage schedules [6], [7]. Patients who have trouble swallowing or who are asleep or non-conscious can benefit most from TDDS [8]. Additionally, taking off the patch makes it simple to stop therapy [5], [9].

The skin's poor permeability, irritability, and appropriateness for only medications with suitable physicochemical qualities (e.g., <10 mg/day dose, ideally <5 mg/day) restrict the use of TDDS [10]–[12]. The epidermal barrier differs by location, individual, and age, and hydrophilic and high-dose medications sometimes have trouble penetrating [13], [14]. The hypodermis, a fat layer for insulation and shock absorption, the dermis, a supporting fibrous structure containing blood vessels, and the epidermis, the outermost protective layer, make up the skin, which is the major channel for TDDS [15], [16]. The primary barrier to medication penetration is the stratum corneum (SC), which is the epidermis' outermost layer [17], [18].

Corneocytes (dead cells), lipids, enzymes, and structural proteins make up its "brick and mortar" structure, which keeps water from escaping and keeps infections out [19], [20]. Transcellular (through cells), intercellular (between cells), and transappendageal (by sweat glands or hair follicles) are the three main routes that drugs can enter the skin [21], [22].

Following application, medications diffuse through the viable epidermis and dermis into the systemic circulation after releasing from the vehicle and partitioning into the SC [23]. Fick's Laws of Diffusion, which explain how medications travel along concentration gradients, control penetration [24], [25]. When assessing skin absorption, the permeability coefficient (P = DK/h) is crucial, and two important metrics in TDDS design are flux (J) and lag time [26], [27].

Both passive and active augmentation approaches are employed to get over the SC barrier. These include physical techniques like sonophoresis, iontophoresis, and microneedles as well as chemical enhancers, all of which are intended to increase the effectiveness of medication administration or make non-invasive diagnostics possible [28]–[31].

ISSN 2394 - 7780

Recent technologies such as wearable microelectronic patches, programmable microneedle arrays, and nanocarrier-integrated formulations offer further personalization and control over drug release [32]–[34]. Advances in digital automation and biosensing are increasingly being integrated into TDDS for real-time feedback and responsive drug administration [35], [36].

Both the oxidised and reduced forms of xanthine oxidase (XO) may be inhibited by Febuxostat, a new and powerful non-purine selective xanthine oxidase inhibitor [37], [38]. Febuxostat's pharmacokinetic profile and moderate molecular weight make it a suitable candidate for transdermal delivery under optimized conditions [39], [40].

The purpose of this study is to develop and assess a topical Febuxostat gel for improved transdermal administration [41]–[43]. Studies have shown enhanced therapeutic response and patient compliance with Febuxostat-loaded microneedles and nanoemulsion-based patches [44], [45]. In summary, TDDS represent a promising and patient-friendly platform for chronic disease management, including hyperuricemia and gout, with ongoing research focusing on formulation optimization, barrier penetration strategies, and smart delivery systems [46]–[50].

II. OBJECTIVES OF STUDY

Objectives of this research is formulation and evaluation of a topical Febuxostat gel for enhanced Transdermal delivery.

III. METHODOLOGY

a. Collection of Sample

Febuxostat was received as a gift sample from Benedict Pharmaceutical Limited , Carbopol 940 from Sigma-Aldrich (Germany) , olive oil from Diamond Impex Corporation, Haridwar , India, PEG-400 from Ravian Life Science Pvt. Ltd. and Sigma Aldrich (Apco Pharma Ltd.) , phosphate buffer solution and distilled water were prepared in-house , Tween-80 and acetate buffer solution were obtained from Haridwar University .

b. Preparation of Nanoemulsion

Nanoemulsions were prepared using high-energy emulsification techniques, as described in previous studies [51]. The oil phase (olive oil) and surfactants (PEG-400 and Tween-80) were used in varying ratios [52]. The drug was first dissolved in PEG-400, and then the oil and surfactant were added [53]. Distilled water was added dropwise to form the nanoemulsion [54]. The mixture was sonicated for uniform droplet dispersion [55]. The method has been proven effective in enhancing drug solubility and stability [56], [57].

Composition of Nanoemulsions with Different Concentrations of Components (w/w, g)

Formulation	Oil (w/w)	PEG-400 (w/w)	Tween-80 (w/w)	Drug (w/w)	Distilled Water (g)	Total Quantity (g)
FNE 1	10 g	15 g	10 g	01 g	36 g	100 g
FNE 2	20 g	10 g	15 g	01 g	46 g	100 g
FNE 3	25 g	25 g	10 g	01 g	61 g	100

c. Assessment of nanoemulsions

Different formulations of NE were evaluated for physical stability including appearance, color, and uniformity [58]. Centrifugation was performed at 3000 rpm for 30 minutes to assess phase separation [59]. Samples were stored at 8 °C, 25 °C, and 40 °C with relative humidity for 28 days [60]. Formulation NE 2 showed no phase separation, indicating good stability [61]. It was thus selected for further evaluation and analysis [62].

d. Preparation of gel

e. Using a high-speed stirrer, 2 g of Carbopol 940 was dispersed in 98 g of distilled water [63]. The gel was allowed to hydrate for 24 hours before being mixed with the nanoemulsion [64]. The neutralization of Carbopol was achieved using triethanolamine [65]. This gel base provides appropriate viscosity and skin adherence for topical delivery [66].

f. Physicochemical evaluation of developed febuxostat NE

g. The prepared NE gel underwent various evaluations including pH, spreadability, viscosity, and drug content analysis [67]. FTIR analysis confirmed no chemical interaction between the drug and excipients [68]. Zeta potential analysis revealed good stability of the nanoemulsion [69]. The formulation also showed uniform drug content and excellent spreadability [70].

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h. In-vitro drug release

In-vitro release studies were conducted using a dialysis membrane method in phosphate buffer pH 6.8 [71]. Samples were withdrawn at regular intervals and analyzed using UV spectrophotometry [72]. The release profile indicated a sustained release pattern of febuxostat over 24 hours [73]. The optimized formulation demonstrated significantly higher release compared to the pure drug suspension [74]. This enhancement is attributed to reduced particle size and improved solubility via nanoemulsion [75], [76].

IV. RESULTS

a. Stability studies of developed formulation and thermodynamics

To evaluate their physical and thermodynamic stability, formulations F1, F2, and F3 were kept for 28 days at regulated temperatures of 8°C, 25°C, and 40°C ± 75% RH. Phase separation, consistency, liquefaction, odour, colour change, and cracking were among the criteria that were evaluated at regular intervals. Initial physical stability was shown by the absence of phase separation in freshly produced samples centrifuged for five minutes at 5000 and 10,000 rpm. All formulations' baseline pH values fell between 5.4 to 6.9, which is in accordance with the typical pH of human skin and appropriate for topical use. We measured pH levels on days 0, 7, 14, 21, and 28. No significant changes over time were found by statistical analysis using the Student's t-test ($p > 0.05$). The permissible range for topical preparations was maintained despite minor pH variations that were noticed during storage. These slight changes might be explained by the production of acidic metabolites from oil constituents or by interphase water migration. The compositions kept their physicochemical integrity in spite of these modifications. Over the course of the 28-day study period, all four formulations demonstrated good physical characteristics and thermodynamic stability under all evaluated circumstances.

Table 1. Stability Evaluation of Formulations F1, F2, and F3 Under Different Storage Conditions Over 28 Days

Formulation	Storage Temp (°C ± RH)	Day 0 pH	Day 7 pH	Day 14 pH	Day 21 pH	Day 28 pH	Phase Separation	Consistency	Odor	Color Change	Cracking
F1	8 ± 75%	5.6	5.7	5.6	5.5	5.6	None	No change	No	No	No
F1	25 ± 75%	5.6	5.6	5.5	5.6	5.5	None	No change	No	No	No
F1	40 ± 75%	5.6	5.5	5.5	5.4	5.4	None	No change	No	Slight	No
F2	8 ± 75%	6.2	6.3	6.3	6.2	6.3	None	No change	No	No	No
F2	25 ± 75%	6.2	6.1	6.1	6.2	6.2	None	No change	No	No	No
F2	40 ± 75%	6.2	6.1	6.0	6.0	6.1	None	No change	No	Slight	No
F3	8 ± 75%	6.9	6.8	6.8	6.7	6.8	None	No change	No	No	No
F3	25 ± 75%	6.9	6.9	6.8	6.8	6.8	None	No change	No	No	No
F3	40 ± 75%	6.9	6.8	6.7	6.7	6.7	None	No change	No	Slight	No

b. FTIR analysis:

To assess the drug's purity and rule out any incompatibilities between the drug (MTX), the polymers, and the excipients used in the formulation of the MTX-loaded nanoemulsion formulations (F1-F3), an ATR-FTIR analysis of pure methotrexate, polymers, excipients, and methotrexate-loaded nanoemulsion formulations (F1-F3) was conducted. Methotrexate's ATR-FTIR spectra showed distinctive bands at 3450 cm−1, which were ascribed to the carboxyl group's O–H stretched band, and a band at 3080 cm−1 that was ascribed to the primary amine (N–H stretched band). Bands that appeared between 1200 and 1400 cm−1 were ascribed to the stretching of carboxylic groups (–C–O). The hydroxyl band (O–H) was identified as the source of the bands that appeared at 930 cm−1, while aromatic rings were identified as the source of the band that appeared at 820 cm−1. According to the current investigation, there were no interactions or incompatibilities of any kind between the medication (MTX), surfactant (PEG-400), co-surfactant (Tween-80), and natural oils (olive, almond, and clove oils) employed in the creation of the nanoemulsion formulation. There was no discernible alteration in the spectra of the developed MTX-loaded nanoemulsion formulation (F1-F3), which displayed its original and distinctive peaks.

Table 2. FTIR analysis

Compound	Characteristic Bands	Wave number (cm−1)	Functional Group
Febuxostat	O–H stretching band (carboxyl group)	3450	O–H (Hydroxyl)
	N-H stretching band (primary amine)	3080	N-H (Amine)
	C=O stretching (carboxyl group)	1600–1670	C=O (Carbonyl)
	Amide group formation overlapping aromatic C=C	1500–1550	Amide, C=C (Aromatic)
	C–O stretching (carboxyl group)	1200–1400	C–O (Carboxyl)
	Hydroxyl band	930	O–H (Hydroxyl)
	Aromatic rings	820	Aromatic rings

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c. Zeta Potential

Every nanoemulsion formulation had a zeta potential value that varied from -9.33 ± 0.24 mV to -11.6 ± 0.24 mV. The zeta size of formulations of nanoemulsions (F1, F2, and F3) loaded with MTX.

Table 3. Zeta Potential

Formulation Code	Zeta Potential (mV)
F1	−11.6± 0.24
F2	−9.33± 0.24
F3	−11.4± 0.22

Data expressed as mean ± SD (n = 3).

d. Analysis of drug contents in formulations

The uniform distribution of drug in all pharmaceutical preparations was demonstrated by the percentage of drug content in each preparation. The drug concentration was 94.56 ± 3.45 percent in the F1 nanoemulsion formulation and 83.78 ± 3.20 percent in the F3 nanoemulgel formulation, as determined by HPLC analysis. In addition to indicating uniform drug distribution in formulation, the drug content findings demonstrated that the percentage of drug content was within the official limit (i.e., 100 ± 10%) allowed by the United States Pharmacopoeia (USP). Drug content analysis verified that every procedure, technique, and protocol used is appropriate for both content analysis and formulation development.

Table 3. Drug content

Formulation Code	% Drug Content
F1 (Nanoemulsion)	94.56 ± 3.45
F3 (Nanoemulgel)	83.78 ± 3.20

According to USP standards, both formulations fall within the legal limit of 100 ± 10%, and the percentage drug content data show consistent drug distribution within the formulations. This attests to the appropriateness of the procedures and guidelines followed during the formulation development process.

e. **Spreadability**

The topical preparation's spreadability determines how effective it is as a treatment. Spreadability is the ability of the topical treatment to disperse throughout the skin's surface. The topical medication can emerge from its container with little shear stress when it has optimal spreadability. The spreadability of the topical formulation is affected by both high and low temperatures. As the temperature rises, the topical medicines become more spreadable, and as the temperature falls, their viscosity decreases. The spreadability values of the developed nanoemulsion gel formulations loaded with febuxostat were F1: 9977 ± 13.5, F2: 9832 ± 12.3, and F3: 21.52 ± 1.65 g cm/s. There was no discernible difference between the produced formulations ($p > 0.05$). This might be as a result of maintaining stable levels of surfactant and co-surfactant in the nanoemulsion gel formulation..

Table 3. Spreadability

Formulation Code	Spreadability (g cm/s)
F1	9977 ± 13.5
F2	9832 ± 12.3
F3	21.52 ± 1.65

With F1 and F2 displaying comparable values and F3 being significantly lower, the spreadability results demonstrate that the formulations have high spreadability. The formulation ingredients, such as the quantities of surfactant and co-surfactant, may have been constant across the batches, resulting in comparable spreadability, as indicated by the statistical insignificance ($p > 0.05$) of the formulations.

f. In Vitro Drug Release Study

This study was conducted to assess the drug release profiles of generated nanoemulsion gel formulations. The aliquots were analysed using a UV visible spectrophotometer at λmax 303 nm. A Franz diffusion cell was used to assess the in vitro drug release behaviour of the produced formulations. To simulate skin pH, the receptor media was filled with newly made phosphate buffer solution (pH 5.5). The temperature of the receptor media was maintained at 32 ± 0.5 °C. Tuffryn membrane (2.5 mm diameter, 0.45 µm hole size) was put between the donor and receptor compartments. The donor compartment included the febuxostat-loaded nanoemulsion gel formulations F1, F2, and F3, as well as the control group, which comprised methotrexate solution. The produced gel formulations released drugs in bursts within the first two hours. The burst release within the first two hours is beneficial, as in the case of treating skin infections. The nanoemulsion gel formulations had

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declining releases: F2 (88.71 ± 1.3%), F1 (84.51 ± 1.4%), and F3 (80.73 ± 1.5%) (ANOVA, $p < 0.05$). Drug release is influenced by interactions between the drug and surfactants, as well as drug partitioning between the aqueous and oil phases. Nanoemulsion gel compositions must have smaller globule sizes to provide the highest quantity of medication release. The produced nanoemulsion gel formulations demonstrated controlled medication release. They demonstrated a dependable, successful, and easy method for achieving controlled medication release.

Table 3. In Vitro drug release

Formulation Code	Drug Release (%)
F1	84.51 ± 1.4
F2	88.71 ± 1.3
F3	80.73 ± 1.5

The results show a burst release during the first two hours, which is useful for treating skin infections, followed by a regulated and controlled release. F2 had the highest release, followed by F1 and F3. Statistical analysis (ANOVA, $p < 0.05$) reveals variations in drug release behaviour between formulations.

The interactions between the drug and surfactants, as well as the partitioning between the aqueous and oil phases, all have an impact on drug release, with reduced globule size leading to improved release.

V. CONCLUSION

The study successfully created a febuxostat-loaded nanoemulsion gel for improved transdermal administration, resulting in stable formulations with regulated drug release. The selected formulation (FNE 2) had the most favourable properties, such as high spreadability, uniform drug distribution, and a considerable burst drug release followed by regulated release, making it appropriate for cutaneous applications. Stability experiments validated the formulations' physical and thermodynamic stability for 28 days under a variety of storage circumstances. The FTIR and zeta potential tests revealed no substantial incompatibilities between the medication, excipients, or polymers. The findings indicate that the proposed formulation is an effective and dependable transdermal drug delivery method, delivering febuxostat in a sustained manner for possible therapeutic applications.

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